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Treatment of Addison's Disease
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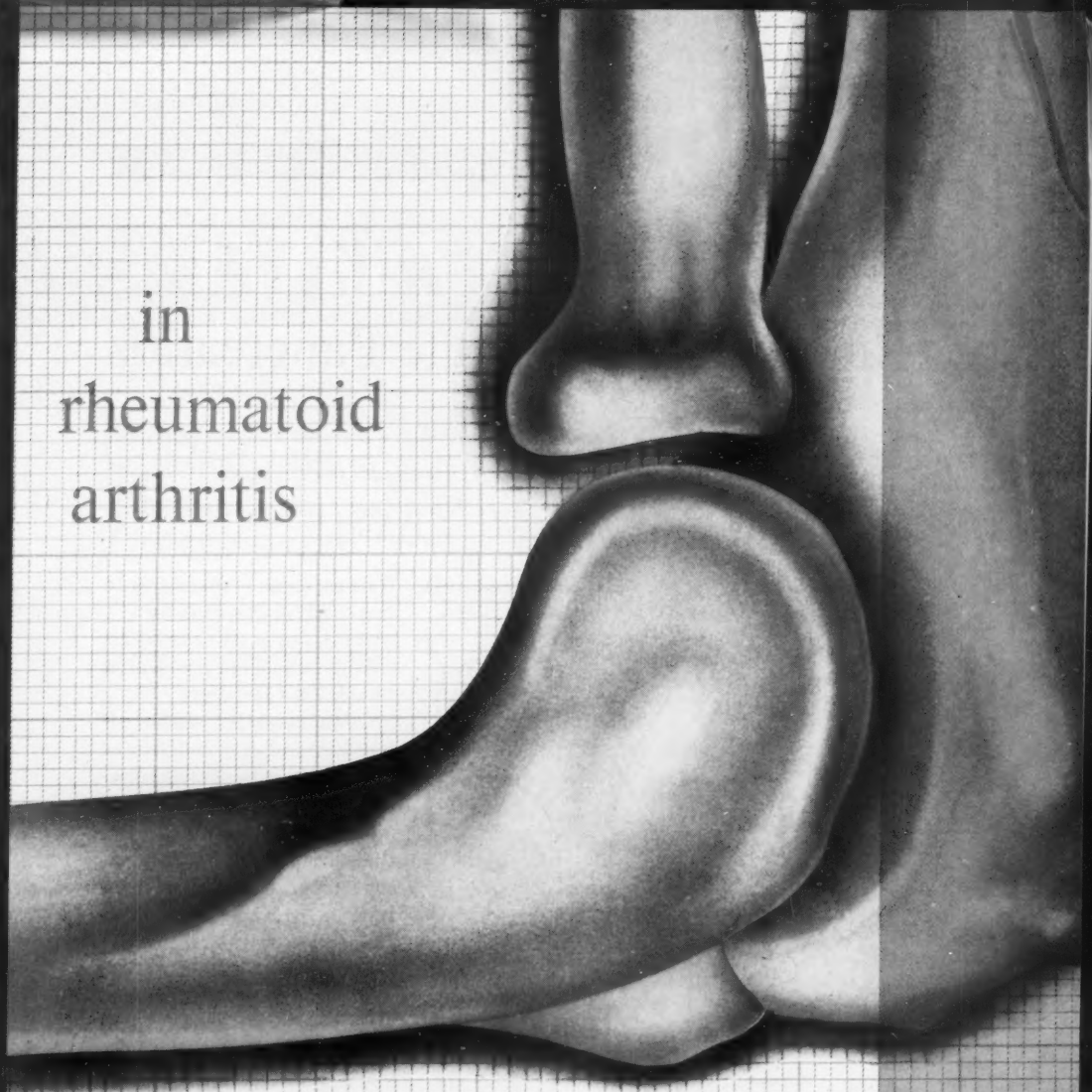

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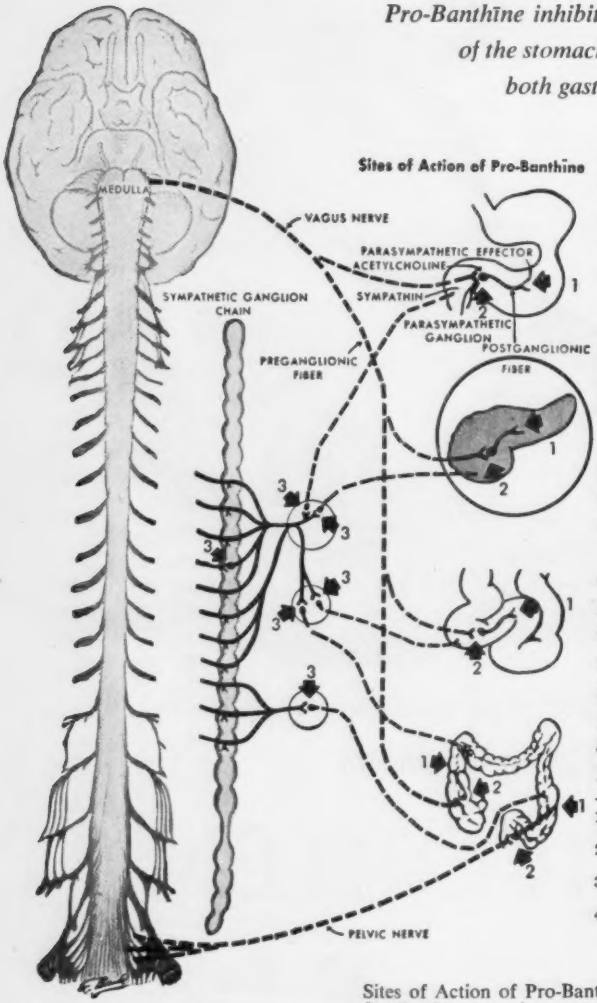

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1. Jones, C. A.: Arch. Int. Med. *96*:332 (Sept.) 1955.
2. Zollinger, R. M.: Postgrad. Med. *15*: 323 (April) 1954.
3. Woodward, E. R.: M. Clin. North America *38*:115 (Jan.) 1954.
4. Schwartz, I. R., and Hinton, J. W.: Personal communication, February, 1955.

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Clinical and Laboratory Studies of Novobiocin, a New Antibiotic

WILLIAM M. M. KIRBY, M.D.
DEAN G. HUDSON, M.D.
and
WARD D. NOYES, M.D., Seattle

Novobiocin is a new antibiotic isolated independently by three different groups of workers.[1] The names given to this antibiotic, and the companies under whose supervision it was discovered, are as follows: Cathomycin (Merck); streptonivicin (Albamycin) (Upjohn); and Cardelmycin (Pfizer). Preliminary in vitro studies have shown that the antibiotic is active against the commonly encountered Gram-positive bacteria and also against certain Gram-negatives.[2] Of particular importance is the fact that staphylococci resistant to other antibiotics are highly susceptible to Novobiocin. Experimental infections in animals have also indicated a high degree of activity with little toxicity.[3] Laboratory studies and a clinical trial in 75 patients comprise the present report.*

Methods

Sensitivity Tests.—Concentrations of novobiocin causing inhibition of growth of streptococci and pneumococci were determined in tryptose phosphate broth containing 3% human blood; 0.5 ml. amounts of a 10^{-4} dilution of an overnight culture were added to equal amounts of broth containing appropriate concentrations of the antibiotic. The cultures were incubated overnight, and the lowest concentration of the antibiotic causing complete inhibition of growth, by gross inspection, was recorded. A similar method was used for staphylococci and B. proteus, except that blood was not added to the broth. With all four organisms, comparisons were also made between the end-points produced by a 10^{-2} and a 10^{-4} dilution of an overnight culture.

Effect of Serum.—These studies were carried out as described above, except that each tube contained a final concentration of 25% sterile horse serum. This was accomplished by diluting the culture in 50% horse serum, so that when 0.5 ml. of this mixture was added to the antibiotic solution the final concentration of serum in each tube was 25%.

Blood Levels After Oral Administration.—Serum concentrations were measured by a serial dilution method; 0.5 ml. of the patient's serum was diluted serially in tryptose phosphate broth through a series of 12 tubes. To each tube, 0.5 ml. of a 10^{-2} dilution in broth of an overnight culture of a standard strain of Staphylococcus aureus was added, and the last tube in which there was complete inhibition of growth was noted after 18 hours of incubation at 37 C. The standard used for calculating the concentrations in unknown serum specimens consisted of a similar row of tubes in which 4γ/ml. of novobiocin in tryptose phosphate broth was similarly diluted. With this standard, containing no serum, inhibition usually occurred in the tube containing 0.12γ/ml. of novobiocin.

Clinical Trial.—Seventy-five patients with a variety of infections caused by Gram-positive bacteria were treated with novobiocin. Most were adults in the older age groups, but five were between the ages of 6 and 12. All patients received

Submitted for publication Feb. 4, 1956.

From the Department of Medicine, University of Washington School of Medicine, and the King County Hospital.

* Sharp & Dohme, Division of Merck & Co., Inc., provided the novobiocin used in this study.

2 gm. daily, 0.5 gm. every six hours. The duration of therapy was in most instances five to seven days, although some patients were treated for as long as two weeks. The patients were seen daily to evaluate the clinical response and to note side-effects.

Results

Sensitivity Tests.—Results of sensitivity tests of representative examples of recently isolated strains are presented in Table 1.

TABLE 1.—*Results of Tube-Dilution Sensitivity Tests of Bacteria Recently Isolated from Clinical Infections*

Organism	Source	Inhibiting Concentration of Novobiocin γ/Ml.
Staphylococcus aureus	Blood	0.5
	Wound	0.1
	Furuncle	0.2
	Wound	0.5
	Urine	1.0
	Wound	0.1
	Abscess	0.05
Group A streptococci	Skin lesion	1.0
	Infected hand	0.3
	Throat	0.3
	Nose	3.0
	Wound	0.5
	Skin	1.0
	Infected eye wound	1.0
	Eye	1.0
	Face wound	1.0
	Elbow abscess	0.5
	Ulcer forearm	1.0
Group D streptococci	Urine	2.5
	Wound abscess	5.0
	Urine	2.5
	Stool	10.0
	Wound	5.0
	Urine	5.0
	Urine	5.0
—	Cervical culture	1.0
Pneumococci	Blood culture	0.5
	Blood culture	0.5
	Sputum	1.0
	Blood culture	0.2
	Throat	2.0
	Nose	0.3
	Sputum	1.0
	Throat	1.0
	Blood culture	0.3
	Sputum	3.0
	Throat	0.5
Proteus	Sputum	5.0
	Wound	5.0
	Urine	5.0
	Throat	5.0
	Urine	5.0
	Urine	5.0
	Throat	10.0
	Throat	10.0
	Blood culture	5.0
	Urine	>10.0
	Urine	5.0
	Urine	>10.0

Of particular interest was the high degree of susceptibility of staphylococci to novobiocin. Of 100 strains of S. aureus tested before novobiocin was used clinically in the hospital, all were inhibited by 1γ/ml or less and 95 failed to grow in 0.5γ/ml. Seventy of these strains were resistant to penicillin, streptomycin, and the tetracyclines, and five were also resistant to erythromycin and chloramphenicol. These results were obtained with a 10^{-2} dilution of an overnight culture. With a 10^{-4} inoculum the end-points were even lower, and a few representative examples are presented in Table 1. Since novobiocin has been used on the wards, 10 strains of S. aureus requiring more than 1γ/ml. for inhibition have been isolated. Of six strains isolated from patients who had received novobiocin for five days or longer, two were inhibited by 5γ/ml. and the other four grew well in 10γ/ml. The other four strains were recovered from patients who had not received novobiocin; three were inhibited by 5γ/ml. and one required 10γ/ml.

Group A streptococci and pneumococci were somewhat less sensitive than staphylococci, but most strains were inhibited by 1γ/ml. or less. The end-points recorded were those observed macroscopically, but subcultures from these tubes on blood agar plates usually showed no growth or only a few colonies. Enterococci (Group D strepococci) were somewhat more resistant than Group A streptococci. All but two strains of B. proteus tested were inhibited by 5γ/ml. or 10γ/ml. of novobiocin.

Effect of Inoculum.—Two to four times as much novobiocin was required to inhibit growth when a 10^{-2} rather than a 10^{-4} inoculum was used. Representative examples of inhibitory concentrations for the smaller as compared with the larger inoculum are as follows: for pneumococci and Group A streptococci the end-point was raised from 1γ to 3γ/ml.; for S. aureus, from 0.2γ to 0.5γ/ml. and for B. proteus from 5γ to 20γ/ml.

Effect of Serum.—In the presence of 25% horse serum, much higher concentrations of novobiocin were required to inhibit growth than when the tests were

performed in broth. With a Group A Streptococcus, for example, the end-point was raised from 2γ to 50γ/ml., and with a Staphylococcus, from 0.5γ to 30γ/ml. The effect of serum on the blood levels was also striking and will be described in the next section.

Serum Concentrations Following Oral Administration.—The patients all received 0.5 gm. of novobiocin every six hours, and blood was obtained two, four, and six hours after a given dose. As can be seen in Table 2, following the first two doses serum concentrations in general were high. There was great variability from dose to dose and from patient to patient, but there were few values lower than 16γ/ml. following the second dose. Most of the levels were much higher than those obtained with the tetracyclines and Erythromycin; the highest level recorded was 128γ/ml.

TABLE 2.—*Serum Concentrations of Novobiocin Following Oral Administration of 0.5 Gm. Every Six Hours*

Patient	Dose Number	Novobiocin in Serum, γ/Ml. After 2 Hr.	After 4 Hr.	After 6 Hr.
1	1	8	4	0
2	1	0	8	4
3	2	-- *	16	--
4	3	128	64	64
5	4	128	64	32
4	7	64	128	128
3	7	32	32	32
2	9	16	16	16
1	9	32	16	8
6	9	16	16	32
7	9	128	64	64
8	10	32	32	16
9	11	16	4	--
10	12	32	16	0
11	12	64	128	64
10	15	32	8	8
12	15	16	32	8
5	15	64	64	64
1	17	8	16	16
13	17	--	--	32
7	17	128	128	128
8	18	64	64	32
6	21	8	32	16
2	21	--	8	--
12	24	4	--	--
2	26	8	16	4
14	31	64	64	--

* Not done.

It should be noted that the standard used in calculating these levels was diluted in broth and not in serum. The effect of serum was clearly apparent, however, in that there was usually slight but definite macroscopic growth in the first three or four tubes containing the patient's serum. Subsequent tubes were completely clear until the end-point was reached. The first four tubes contained 25%, 12%, 6%, and 3% of the patient's serum, respectively. It was evident, therefore, that serum counteracted the growth-inhibiting effect of the antibiotic but that the drug could be diluted out to a remarkable degree and produced complete macroscopic inhibition of growth when the concentration of serum was less than 3%. With a concentration of 128γ/ml., for example, there was inhibition of growth through the ninth tube, in which the serum dilution was 1:1024. This suggests a loose binding of the antibiotic to the serum proteins which does not prevent the drug from exerting its inhibitory effect in high dilutions of serum.

Clinical Results

A summary of the 75 patients treated, and the response to therapy, is presented in Table 3. A more detailed consideration of the results of each group of patients will be presented below.

TABLE 3.—*Clinical Results in Seventy-Five Patients Treated with Novobiocin*

	Total Cases, No.	Good	Indeterminate	Poor
Bacterial pneumonia	35	28	5	2
Bacteremia	3	1		2
Staphylococcal infections	28			
Wound infections	15	12	3	
Abscesses and furuncles	4	2	2	
Urinary tract	4	2	2	
Bacteremia	2	2		
Pyogenic arthritis	1		1	
Streptococcal infections	3			
Wound	1	1		
Erysipelas	1	1		
Tonsillitis	1	1		
Miscellaneous	11			
Cellulitis (no organism)	2	2		
Lung abscess	2		2	
Diphtheria	1	1		
Respiratory	6		6	
	75			

Bacterial Pneumonia.—The 35 patients with bacterial pneumonia were mostly adults in the older age groups, many of whom were debilitated and had other diseases.

More than half were chronic alcoholics. Studies with several antibiotics over the past few years have given us some insight into the type of response that may be expected in this group of patients. Although pneumococci were the predominant organisms in sputum cultures of only half the patients, it is probable that all 35 patients had pneumococcal pneumonia. Except for the three with positive blood cultures, the patients were all regarded as moderately ill. In the 28 who were considered to have a good response, there was a definite decrease in fever, toxicity, and cough and sputum during the first 48 hours, and these patients were all afebrile within 5 days. In some patients novobiocin was discontinued at the end of five days, but in most it was administered for seven. The subsequent course was uncomplicated, and x-ray clearing was complete within three to four weeks. In the five patients whose response was regarded as indeterminate there were signs of clinical improvement within the first 48 hours, but the temperature remained elevated for from 7 to 12 days. In two of these five patients, sterile pleural effusions formed, and these probably contributed to the prolonged fever. Although the response was classified as indeterminate, this same sequence of events has occurred with other drugs, including penicillin. Of the three patients with bacteremia, one showed a good clinical response and was afebrile within five days. The other two continued to show signs of toxicity and to have a temperature varying from 101 to 103 F daily. In both instances a second blood culture was drawn on the fourth day and the patient was then put on large doses of penicillin. Blood cultures in both cases were negative. In one case the temperature became normal on the 10th day, and there was slow resolution of the x-ray infiltrates. Sputum of the other patient, an 85-year-old man, revealed a pure culture of Gram-negative rods on the seventh day, and he died a day later. Although the response in these two cases was classified as poor, it should be noted that the same sequence of events has been observed in patients treated with other antibiotics.

Staphylococcal Infections.—Evaluation in these cases was especially difficult. In most instances therapy with novobiocin was started at the time of drainage of wounds or abscesses, and it was therefore difficult to determine whether the response could be attributed to the antibiotic. The prompt subsidence of fever and toxicity in almost all cases was impressive, however, and did appear to indicate that there was a definite therapeutic effect. The impression gained from the 26 cases was that the response was comparable to that observed three years previously, when a similar group of patients was treated with erythromycin.[4] Most wound infections and abscesses had healed within 5 to 10 days. In five cases, however, the infection persisted despite initial improvement, and organisms cultured after 7 to 10 days were resistant to 5γ or 10γ/ml. of novobiocin. These patients were then treated with other antibiotics and slowly recovered. The two patients with positive blood cultures might be expected to provide more decisive information, but here again the presence of complicating factors made evaluation difficult. One was a 65-year-old woman with pancreatitis who had run a septic course and had had blood cultures repeatedly positive for Staphylococcus aureus during the preceding month. Her temperature had gradually declined and remained at about 100 F after treatment with chloramphenicol and erythromycin was stopped. When novobiocin was started she had received no antibiotics for 10 days, during which time three blood cultures had been positive. During 12 days of novobiocin therapy her temperature subsided to normal, and repeated blood cultures following cessation of cathomycin were negative. Novobiocin seems to have exerted a definite effect in this case, although the infectious process seemed to be subsiding despite the presence of positive blood cultures, and the result is therefore not too clear-cut. The other patient was a 10-year-old boy with a subhepatic abscess which formed after sur-

gery for a lacerated liver. After several weeks of only partially successful therapy with erythromycin and chloramphenicol, a blood culture was positive for staphylococci sensitivity only to bacitracin. After he had received bacitracin for 3 days and novibiocin for 17, the temperature was somewhat lower and blood cultures were negative, but signs of infection persisted and staphylococci resistant to novobiocin were cultured from the liver. In this instance, novobiocin seems to have exerted a suppressive effect, and failure to eradicate the infection was probably due to the presence of multiple liver abscesses.

Streptococcal Infections.—The clinical response in all three cases seemed good. Particularly striking was the response in the patient with erysipelas. This was a 56-year-old woman with erysipelas involving her entire face, who had a temperature of 103 F and was very toxic and uncomfortable. Redness and pain subsided within 48 hours, and the temperature was normal on the fifth day after starting novobiocin. Comparisons are difficult, but the response in this case seemed equivalent to that observed in cases treated with penicillin or erythromycin.

Miscellaneous.—In two patients with cellulitis of the lower extremity the response to novobiocin appeared good. The two lung abscess patients showed continued improvement on novobiocin, but the effect of the antibiotic was difficult to assess. Six patients with congestive heart failure and signs of accompanying pulmonary infection showed prompt improvement, but the results were regarded as indeterminate, since some of the improvement was due to the treatment of the congestive failure.

Side-Effects

There was remarkable freedom from side-effects. Two patients complained of nausea, but this was transient and did not necessitate stopping the drug. One patient with chronic pyelonephritis and uremia noted dizziness and blurring vision approximately an hour after receiving 0.5 gm. of novobiocin. This occurred on three occasions, following which the antibiotic was discontinued. This case is not included among the 75 in which the results of therapy were evaluated. Two patients developed maculopapular rashes, which subsided within five days. Both patients were also receiving potassium iodide, and it is therefore not certain that the rashes were caused by novobiocin. Twenty of the seventy-five patients had blood cell counts performed after novobiocin was discontinued, and in all of them the blood cell count was normal.

Comment

Novobiocin possesses a number of interesting and unique characteristics. Particularly important is the high degree of susceptibility of staphylococci to this antibiotic, with a complete lack of cross resistance with other antibiotics. Pneumococci and Group A streptococci are inhibited by relatively low concentrations (1γ to 2γ/ml.) but are less sensitive than staphylococci. This is in contrast to the situation occurring with penicillin, erythromycin, chloramphenicol, and the tetracyclines, where pneumococci and Group A streptococci are more sensitive than staphylococci. Among the Gram-negatives, it is of interest that members of the Proteus group are quite susceptible to novobiocin, being inhibited by 5γ to 10γ/ml.

In vitro observations of novobiocin which might limit its clinical usefulness are the fact that resistance of staphylococci develops rapidly and that the antibiotic is less active when there is an increase in the size of the inoculum of bacteria. Of even more importance is the marked decrease in activity in the presence of serum. More than 90% of novobiocin appears to be bound by serum proteins; consequently, the concentrations required to inhibit growth are much higher in serum than in broth. Tompsett, Shultz, and McDermott studied this phenomenon in detail with penicillin K, which is bound to approximately the same

degree as novobiocin.[5] As determined in the present study, concentrations of novobiocin in the serum of patients receiving 2 gm. daily were remarkably high. It is important to note, however, that these levels were determined by a serial dilution method in broth and do not take into account the factor of serum inhibition. The probable importance of serum inhibition was indicated by the slight but definite growth in the first few tubes, containing 12% to 25% of the patient's serum, even though there was complete suppression of growth in subsequent tubes as the serum was diluted out.

The clinical results were in general favorable, although evaluation was extremely difficult. Novobiocin clearly exerted a therapeutic effect, but the magnitude of its action was difficult to assess. The response in patients with bacterial pneumonia and with staphylococcal infections appeared to be similar to that observed with erythromycin. The high degree of sensitivity of staphylococci to novobiocin, and the high blood levels obtained, caused us to hope that the clinical results might be considerably better than those observed with erythromycin. This did not seem to be the case, however, and this is probably due to the fact that the role of serum inhibition is important in the patient as it is in the test tube.

A factor which will undoubtedly limit the usefulness of novobiocin is the rapidity with which staphylococci develop resistance to the antibiotic in patients. With most soft tissue infections healing occurred in 5 to 10 days and bacteria were promptly eradicated from the lesion. With more indolent infections, however, the organisms became resistant after several days of therapy, and the patient failed to show a further clinical response. This occurred in five patients with abscesses or wound infections and in a patient with positive blood cultures who probably had multiple liver abscesses.

On the basis of these observations, two recommendations concerning the use of novobiocin would appear to be indicated. The first is that novobiocin should be used exclusively for the treatment of staphylococcal infections, particularly when the causative organism is resistant to other antibiotics such as penicillin, streptomycin, and the tetracyclines. The other recommendation is that novobiocin should be administered in conjunction with another antibiotic in an attempt to prevent or delay the emergence of antibiotic-resistant staphylococci. Antibiotics which might be given simultaneously are erythromycin, chloramphenicol, and bacitracin, since these are the ones to which hospital-acquired staphylococci are still often susceptible. The use of novobiocin solely for staphylococcal infections seems warranted, since it appears to possess no advantages over other chemotherapeutic agents in the treatment of other types of infections. Streptococci and pneumococci have not become resistant to other antibiotics which are equally or more effective. The usefulness of novobiocin in treating urinary tract infections caused by organisms of the Proteus group has not been evaluated in the present study. Unless the results are striking, however, it is our opinion that novobiocin should be reserved for the treatment of staphylococcal infections.

Summary and Conclusions

The results of laboratory and clinical studies of a new antibiotic, novobiocin, are presented. Staphylococci were remarkably sensitive in vitro, and there was no cross resistance with other antibiotics. Pneumococci and Group A streptococci were also inhibited by low concentrations, but they were less sensitive than staphylococci. Among the Gram-negative bacilli, members of the Proteus group were moderately sensitive.

Novobiocin was less effective in the presence of a larger inoculum of bacteria, and serum exerted a marked inhibitory effect. Serum concentrations performed by dilution of patients' serum in broth were

considerably higher than those obtained with other antibiotics, although the method used did not reflect the factor of serum inhibition. The daily dose was 2 gm., administered orally, and side-effects were minimal. Two patients developed rashes which may have been caused by novobiocin.

Results in 75 patients with a variety of clinical infections were in general favorable, and they appeared comparable to those obtained with erythromycin. In staphylococcal infections where prompt healing did not occur, the infecting organisms rapidly became resistant to novobiocin. For this reason, it is recommended that novobiocin be used exclusively for the treatment of infections caused by antibiotic-resistant staphylococci. Wherever possible, another antibiotic to which the organism is also sensitive should be administered simultaneously.

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Severe Liver Disease Complicated by Bacteremia Due to Gram-Negative Bacilli

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A recent review [1] of the records of 137 patients with bacteremia due to Gram-negative bacilli disclosed that 4 of the 137 patients had severe disease of the liver. This association seems more than coincidental and supports the views of Whipple and Harris.[2] These authors reported four cases of Laennec's cirrhosis in which there was septicemia due to Escherichia (Bacterium) coli and postulated that a deficiency of effective reticuloendothelium in the cirrhotic liver, or changes in hepatic circulation, may account for the occurrence of septicemia in cirrhosis. Spellberg [3] and Beeson [4] have also commented on infections of the blood stream due to colon bacilli in patients with cirrhosis of the liver.

The purpose of our report is to describe four cases of severe hepatic disease complicated by bacteremia due to Gram-negative bacilli, in order to emphasize this complication further.

Report of Cases

CASE 1.—A 45-year-old man was admitted to the Mayo Clinic on Feb. 19, 1946. He had been in apparent good health until approximately six months previously, when he began to notice swelling of the abdomen, anorexia, and generalized weakness. Three months prior to admission he began to have vague left upper abdominal pain and his urine became dark. One month prior to admission icterus and pruritus developed. He had occasional vomiting after meals and his stools became lighter in color. Two weeks prior to admission he had a shaking chill with the onset of fever(temperature up to 105 F). The jaundice deepened, and a few days prior to admission the patient became drowsy and at times irrational. There was a history of heavy intake of alcohol during a period of 15 years.

Physical examination revealed an icteric somnolent man who appeared to be chronically ill. Other pertinent physical findings included a blood pressure of 98/66. The liver was palpable 3 fingerbreadths below the right costal margin, and the spleen also was palpable. The abdomen was tense, and there was a so-called fluid wave. Spider angiomas were noted on the skin overlying the left shoulder. The patient had nystagmus, apparently congenital in origin. The temperature at the time of admission was 103 F.

The results of laboratory examination were as follows: urinalysis, negative; hemoglobin, 10.9 gm. per 100 cc. of blood; erythrocytes, 3,220,000, and leucocytes, 7200 per cubic millimeter of blood; flocculation reaction for syphilis, negative; direct-reacting bilirubin, 23.6 mg., and indirect-reacting bilirubin, 1.7 mg. per 100 cc. of serum; sedimentation rate of erythrocytes, 80 mm. in one hour (Westergren method); prothrombin time, 29 seconds; cholesterol, 150 mg., and cholesterol esters, 43 mg. per 100 cc. of plasma.

Roentgenograms of the chest did not disclose any abnormality.

The patient's course in the hospital was marked by spiking temperatures ranging up to 103 and 104 F initially. For this reason, blood was obtained for culture on Feb. 23; the cultures grew out Salmonella, species undertermined (eight colonies per cubic centimeter). On in vitro testing, the organism was sensitive to streptomycin in concentrations ranging from 12 to 25 units of the drug per cubic centimeter. Also other blood cul-

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tures, obtained on Feb. 25, grew out Salmonella, species undetermined (10 colonies per cubic centimeter).

Treatment with streptomycin, 2 gm. a day administered by the intramuscular route, was started on Feb. 23 and continued through March 3. The patient remained febrile throughout his course, becoming increasingly jaundiced and edematous. He had respiratory distress and died on March 5, 1946.

Necropsy.—The body was severely jaundiced, and there was edema of the hands and feet. The peritoneal cavity contained about 700 cc. of clear bile-stained fluid, and the right pleural cavity contained about 100 cc. of clear yellow fluid.

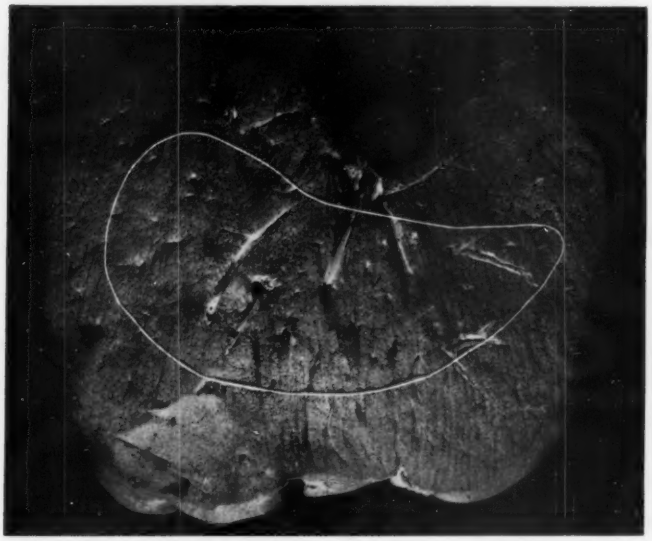

Fig. 1 (Case 1).—Hypertrophy of the liver (3373 gm.); fatty change and granularity were apparent.

The heart was enlarged and weighed 476 gm. (normal, 390 gm.) but was otherwise normal. The lower lobes of the lungs were edematous. The spleen was hypertrophied and weighed 965 gm. (normal, 150 gm.). The liver was hypertrophied and weighed 3373 gm. (normal, 1800 gm.). The surface was finely granular (Fig. 1) and tannish green. The consistency appeared normal. The cut surface was yellowish green.

The mucosa of the lower third of the esophagus was ulcerated, and a small ruptured venule could be seen. The stomach contained about 300 cc. of dark, brownish material as well as large clots of blood. The kidneys were enlarged, weighing 547 gm. (normal, 390 gm.), and were markedly stained with bile.

Histologic examination revealed focal hemorrhages into the alveoli of the lungs. In the spleen there were dilated sinuses, increased connective tissue, and numerous giant cells. In sections of the liver the normal parenchyma was replaced by poorly defined nodules of regeneration only partially separated by narrow zones of connective tissue. There were increased numbers of bile ducts, canaliculi, and lymphocytes in the internodular zones. The cells of the regenerative nodules had undergone severe alcoholic hyaline degeneration and mild fatty degeneration. Scattered throughout the parenchyma were numerous focal collections of lymphocytes, phagocytes, and polymorphonuclear cells. In some of these collections the polymorphonuclear cells predominated so that they presented the appearance of small abscesses, whereas in others the phagocytes predominated so that they presented a granulomatous appearance (Fig. 2).

In sections of the esophagus there was evidence of numerous recent ulcers with erosion of small venules. Dilated veins (varices) were also present, but these were not eroded. In sections of the kidneys there was a mild increase in the number of endothelial cells of the glomerular capillaries. Pigmentation, degenerative changes, and necrosis were observed in the tubular epithelium, particularly in the region of the corticomedullary junction. There were focal collections of lymphocytes and polymorphonuclear cells adjacent to the degenerating tubules. Many of the tubules were dilated, and some contained pigmented debris and crystalline material. There were also areas with atrophy of the tubules, increase of connective tissue, and lymphocytes. Sections of the testes revealed moderate atrophy of the tubules.

The following anatomic diagnoses were made:

alcoholic cirrhosis of the liver with hypertrophy (3373 gm.; normal, 1800 gm.); Salmonella septicemia (clinical); hypertrophy of spleen (965 gm.; normal, 150 gm.); varices of esophagus with rupture and hemorrhage (300 cc.); icterus, severe; edema of lungs; hypertrophy of kidneys (547 gm.; normal, 390 gm.), with lower nephron nephrosis; hypertrophy of heart (476 gm.; normal, 390 gm.) (hypertension); ascites (700 cc.); hydrothorax (right, 100 cc.); atrophy of testes.

CASE 2.—A 32-year-old white woman was admitted to the Mayo Clinic on Feb. 25, 1950, complaining of generalized weakness of one year's duration and jaundice of nine months' duration. She had been in good health until March, 1949, when fatigue, anorexia, and increase in pigmentation of the skin developed. In May she had several episodes of shaking chills. Also in May she received treatment elsewhere for possible Addison's disease and was given intravenous injections of an unknown type. The treatment seemed to alleviate her symptoms temporarily; however, in July jaundice appeared and gradually increased. Ultimately, a diagnosis of disease of the liver was made and she was advised to eat a diet high in protein and carbohydrate and moderate in fat with extra vitamins; subsequently there was some abatement of the jaundice. She did fairly well until January, 1950, when phlebitis of her right leg developed and she was hospitalized, during which time she underwent blood transfusion. Following improvement of the phlebitis marked anorexia with nausea and general malaise again developed. Weakness and jaundice increased, and the patient came to the clinic for further evaluation of her illness.

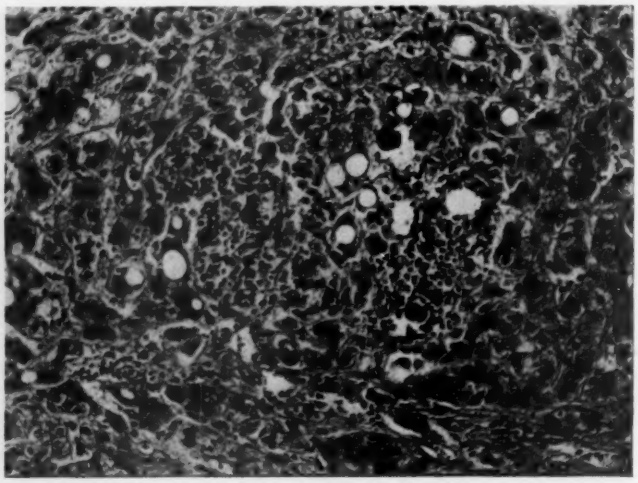

Fig. 2 (Case 1).—Degenerative changes in liver cells and focal collections of polymorphonuclear leucocytes and phagocytes. Hematoxylin and eosin; × 140.

On physical examination she had a temperature of 101.6 F. She was severely jaundiced and had increased pigmentation of the skin. The edge of the liver was palpable 4 cm. below the right costal margin and was tender. The spleen was palpable 5 cm. below the left costal margin, and it also was tender. The abdomen was distended, and there was a so-called fluid wave.

The results of laboratory examination were as follows: urinalysis, Grade 2 albuminuria and evidence of bile in the urine; hemoglobin and cells in the blood, values within normal limits; sedimentation rate, 111 mm. in one hour (Westergren method); urea, 28 mg. per 100 cc. of blood; blood sugar (fasting), 86 mg. per 100 cc.; direct-reacting serum bilirubin, 9.8 mg., and indirect-reacting bilirubin, 2.4 mg.; serum proteins, 9.7 gm. per 100 cc., with an albumin-globulin ratio of 2:7.7; cephalin-cholesterol-flocculation test of liver function, 3+; thymol turbidity test of liver function, 10 units; cholesterol, 63 mg., and cholesterol esters, less than 20 mg.; prothrombin time, 33 seconds; the urinary excretion of 17-ketosteroids (Feb. 26), 4.3 mg. per 24 hours, and Kline flocculation test for syphilis, negative.

Roentgenograms of the chest did not disclose any abnormality.

Because of spiking temperatures to 105 F and chills, blood was obtained for culture on Feb. 26 and 27. These cultures grew out E. coli, which was sensitive to streptomycin in a concentration of 6.25γ per cubic centimeter and to oxytetracycline in a concentration of 3.12γ per cubic centimeter.

Oxytetracycline, 500 mg. every six hours, was administered by the oral route beginning on Feb. 28, in addition to supportive measures for hepatic disease. By March 2 the temperature had become normal, and cultures of blood obtained on March 1, 2, 4, and 6 gave negative results. Treatment

with oxytetracycline was continued through March 8, the temperature having been normal from March 2 through March 8. Treatment with oxytetracycline was discontinued on March 8, and the patient remained afebrile, although the jaundice persisted. On March 25 she had a shaking chill followed by a temperature of 102 F. Culture of the blood on March 28 and 30 and on April 1 gave negative results. Treatment with oxytetracycline was reinstituted empirically on March 27 in a dose of 500 mg. every six hours given orally and was continued despite the negative results of culturing the blood. By March 29 the temperature was again normal and remained so throughout the patient's hospitalization. Treatment with oxytetracycline was continued in reduced dosage of 250 mg. every six hours through April 9. The jaundice fluctuated somewhat during the remainder of the hospitalization, with some tendency to decrease following improvement in the latter febrile episode.

Because of uncertainty as to the cause of the jaundice and the possibility that a previously described nonfunctioning gall bladder was a source of infection accounting for the bacteremia, abdominal exploration was carried out on April 10, 1950. The liver was found to be greatly enlarged with diffuse multiple soft nodular areas, a biopsy of which disclosed postnecrotic cirrhosis, Grade 3, with wide zones of liver-cell destruction and replacement by inflammatory cells, chiefly plasma cells. However, the gall bladder was greatly distended, and a short-circuiting procedure, an end-to-side cholecystogastrostomy, was performed. The postoperative course of the patient was not further complicated, but there was little improvement in her general condition. At the time of dismissal from the hospital, on April 24, 1950, she was still jaundiced, with a value of 6.4 mg. for direct-reacting serum bilirubin and a value of 1.4 mg. for indirect-reacting bilirubin. Upon her return home she had a progressive downhill course and died on Aug. 14, 1950. Necropsy was not performed.

Case 3.—A 20-year-old youth came to the Mayo Clinic on June 6, 1953, because of fever of undetermined origin.

He recounted that four or five years prior to admission he had experienced a febrile episode with cough and chills associated with jaundice. The jaundice had persisted to the time of admission, despite periods of hospitalization and extra rest in bed. About a year prior to admission he began to have edema of the legs, which persisted. Four months prior to admission he had thrombophlebitis in the right leg. Four days prior to admission a fever with shaking chills developed. The patient's mother also had had transient jaundice at about the time the patient originally became ill.

Physical examination revealed a jaundiced youth appearing older than the stated age of 20. Other pertinent findings included temperature of 103 F, spider angiomas on the neck and upper part of the back, and petechial lesions in the mucous membrane of the palate and pharynx. The abdomen was distended, and there was a so-called fluid wave. The edge of the liver was not palpable; however, the spleen was palpable on deep inspiration. There was pitting edema of the ankles, and the nail beds appeared pale.

Laboratory data were as follows: urinalysis, negative; hemoglobin, 11.4 gm.; erythrocytes, 4,520,000; leucocytes, 13,000; differential count: 22.5% lymphocytes, 4% monocytes, 68.5% neutrophiles, 2% eosinophiles, and 3% metamyelocytes; platelets, 54,000; sedimentation rate, 21 mm.; blood urea, 40 mg.; blood sugar (fasting), 83 mg.; direct-reacting serum bilirubin, 16.88 mg., indirect-reacting bilirubin, 2.12 mg.; cholesterol, 117 mg., and cholesterol esters, 35 mg.; serum proteins, 5.67 gm. (albumin, 2.37 gm.; globulin, 3.30 gm.); Kline flocculation for syphilis, negative; prothrombin time, 29 seconds; cephalin-cholesterol-flocculation test of liver function, 3+; special examination of a blood smear showed numerous macrocytes and a reduction in number of platelets.

The roentgenographic appearance of the chest was normal.

The patient continued to display a spiking temperature curve, and on June 8 blood was obtained for culture. These cultures showed E. coli, 60 colonies per cubic centimeter. The organism was sensitive to streptomycin in a concentration of 12.5γ per cubic centimeter and to oxytetracycline in a concentration of 1.5γ per cubic centimeter. Cultures of the blood on June 9 again disclosed E. coli. On June 9 the patient was given oxytetracycline, 750 mg. every 6 hours by the oral route, and dihydrostreptomycin, 1 gm. every 12 hours by the intramuscular route. He never became completely afebrile, although the temperature reached much lower levels after June 10. Between June 10 and June 24 the temperature did not exceed 100 F. Treatment with oxytetracycline and streptomycin in the above dosage was continued through June 21. Cultures of blood obtained on June 11, 12, and 13 gave negative results, but on June 14 cultures of the blood again showed E. coli., one colony per 3 cc. Cultures of the blood obtained on June 16, 17, 22, and 23 gave negative results.

After treatment for the bacteremia the patient felt somewhat better, although there was no apparent improvement in his hepatic status. It was felt that he had severe hepatic insufficiency secondary to cirrhosis of the liver, which probably was on the basis of chronic hepatitis.

Special studies were carried out on the organisms isolated from this patient's blood. On June 11, two

days after initiation of combined dihydrostreptomycin-oxytetracycline therapy, blood was drawn and tests were carried out against the E. coli isolated, which demonstrated that the patient's serum containing the above antibiotics gave a complete bactericidal effect in a dilution of 1:4. In addition, other in vitro tests indicated that oxytetracycline, 100γ per cubic centimeter, or streptomycin, 12.5γ per cubic centimeter, was bactericidal. Further tests indicated that a combination of oxytetracycline, 6.25γ per cubic centimeter, and streptomycin, 6.25γ per cubic centimeter, also was bactericidal, indicating at least an additive effect.

The patient was dismissed from the hospital on June 25, 1953, but it was thought that his future was precarious. Dr. Stephen B. Thorson, of Calgary, Alberta, Canada, wrote that the young man

findings included a Grade 2 soft, systolic midprecordial murmur without extensive radiation, abdominal distention and tympanites, extension of the edge of the liver to a level 1 fingerbreadth below the right costal margin, and pitting edema of the ankles.

Laboratory data were as follows: urinalysis, negative except for Grade 1 albuminuria; hemoglobin, 12.2 gm.; erythrocytes, 2,370,000; leucocytes, 3600; differential count: 56% lymphocytes, 4% monocytes, 27% neutrophiles, 12% bands, and 1% eosinophiles; blood urea, 28 mg.; direct-reacting serum bilirubin, 2.5 mg., and indirect-reacting bilirubin, 1.8 mg.; prothrombin time, 56 seconds; blood smear: scattered macrocytosis with increased regeneration of erythrocytes and immaturity of myeloid cells; tuberculin skin test, negative.

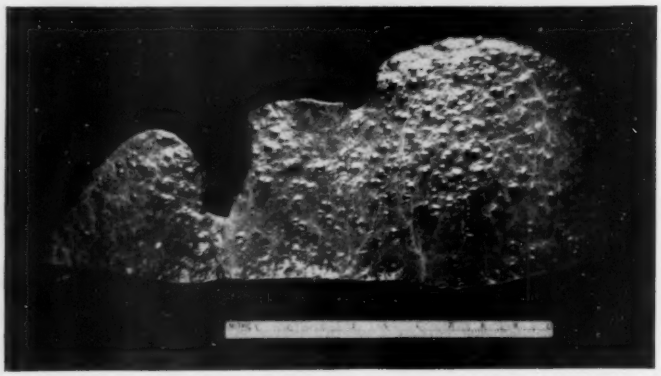

Fig 3 (Case 4).—Note small widely separated nodules on surface of liver.

died on July 18, 1953, in hepatic coma. Permission for necropsy was not obtained.

Case 4.—A 7-year-old girl came to the Mayo Clinic on Aug. 17, 1954, because of jaundice and fever that she had had for three weeks. At the age of one month she had had jaundice of undetermined cause. She was well thereafter until the latter part of July, 1954, when she had chronic fatigue and occasionally complained of vague abdominal pain. Subsequently she began to have anorexia and to vomit, became jaundiced, and had edema of the ankles and ascites. Treatment elsewhere consisted of rest in bed and a diet high in protein and carbohydrate and moderate in fat, with vitamins added. She did fairly well on this regimen until Aug. 14, when chills and a temperature up to 103 F developed, with increasing abdominal pain and backache. By paracentesis elsewhere, on Aug. 16, two pints (about 1 liter) of fluid was removed. The anorexia and jaundice progressed, and the child was referred to the clinic for further evaluation.

Physical examination revealed a pale jaundiced child with a temperature of 102 F. Other physical

The roentgenographic appearance of the chest was normal, but roentgenograms of the abdomen indicated scattered pockets of gas in the stomach and intestines and homogeneous density low in the abdomen suggestive of ascites. An electrocardiogram did not disclose any abnormality.

Treatment was supportive. Because of the continued febrile course with spikes of temperature ranging up to 102 F, blood was obtained for culture on Aug. 18; the culture grew out E. coli, which was sensitive in vitro to streptomycin in a concentration of 25γ per cubic centimeter and to the tetracycline group in a concentration of 1.5γ per cubic centimeter. Therapy with dihydrostreptomycin, 0.5 gm. every 12 hours administered by the intramuscular route, was started on Aug. 18. Oxytetracycline was started on Aug. 20 in a dose of 250 mg. administered intravenously every four hours.

The temperature gradually subsided to lower levels, and from Aug. 21 it remained at 99 F, or less. However, the course of the patient was gradually downhill, with increasing abdominal distension

and jaundice. She became comatose and died on Aug. 26.

Cultures of the blood on Aug. 20 and 24 gave negative results.

Necropsy.—The body was severely jaundiced, and there was edema of the legs. The peritoneal cavity contained about 5000 cc. of yellow fluid in which there were some clumps of fibrin. There was 50 cc. of yellow fluid in the pericardial cavity.

There were edema, congestion, and hemorrhages in both lungs. The spleen was enlarged and weighed 185 gm. (normal, 66 gm.). The pulp of the spleen appeared congested. The liver weighed 185 gm. (normal, 66 gm.). The pulp surface was studded with small widely separated nodules (Fig. 3). The liver cut with increased resistance, and on the cut surface also there were numerous small nodules that measured up to 5 mm. in greatest diameter. Many of the nodules appeared yellow, whereas the remainder of the liver appeared green. Dilated lymphatics were visible in Glisson's capsule.

In the upper third of the esophagus there were patchy areas of ulceration. Small varices could be seen in the lower portion of the esophagus. The small and large intestines were edematous, and there were several subserosal ecchymotic areas in the small intestine. There were also multiple small petechiae in the mucosa of the bowel. All of the connective tissue in the abdominal cavity appeared edematous. All the abdominal lymph nodes examined were enlarged, soft, and yellow. The kidneys were enlarged, weighing 290 gm. (normal, 140 gm.). There were numerous dilated veins and submucosal hemorrhages in the urinary bladder. There was a cyst of the pineal gland, with compression of the third ventricle.

Histologic examination revealed separation of the muscle fibers of the myocardium, as if by edema. There were focal edema and hemorrhages into the alveoli of the lungs and severe congestion of the pulp of the spleen.

Examination of the liver revealed that the normal parenchyma was entirely replaced by regenerative nodules of varying size, with none of them more than 5 mm. in greatest diameter. These nodules were separated from one another by relatively narrow internodular zones of fibrous connective tissue and some broad zones of atrophy in which liver cells were destroyed and only ducts, sinusoids, and leucocytes remained. There were relatively large numbers of polymorphonuclear leucocytes in these internodular zones and in the peripheral portion of the regenerative nodules (Fig. 4). The regenerative nodules had produced marked venous compression and distortion. The parenchyma of the regenerative nodules consisted of relatively large cells arranged in ill-defined laminae that generally were two cells or more in thickness. In many of these cells there was evidence of fatty or acidophilic degeneration, and in many there were pigment granules. Sections stained by the Brown-Gram technique for bacteria failed to reveal any micro-organisms. Many of the bile capillaries were plugged with bile. At the periphery of some of the regenerative nodules, degenerative changes were much more severe and were attended by the presence of large numbers of polymorphonuclear cells. Some of the smaller regenerative nodules appeared to be entirely overrun by leucocytes.

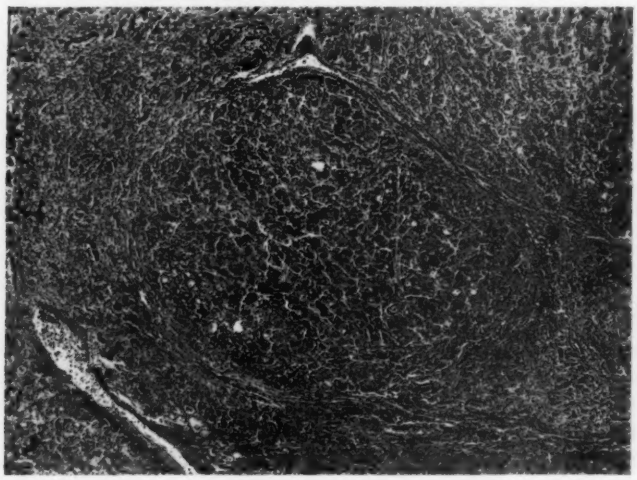

Fig. 4 (Case 4).—Regenerative nodule. Note leucocytes at periphery and in internodular zones. Hematoxylin and eosin; × 50.

There was histologic evidence of recent ulceration of the mucosa in the upper part of the esophagus, which extended into the muscularis layer.

The entire thickness of the esophageal wall was infiltrated with lymphocytes and polymorphonuclear cells, which extended far beyond the immediate neighborhood of the ulcer. Leucocytes were particularly numerous in the walls of the blood vessels. A similar ulcer in the lower portion of the esophagus had eroded a number of venules. Some of the larger vessels were thrombosed but had not been eroded.

In sections of the kidneys there was a mild increase in endothelial cells in the glomerular capillaries. There were degenerative changes, pigmentation, and sloughing of the epithelium of the tubules, particularly those of Henle's loop. There was much pigmented debris in these and the collecting tubules.

The following anatomic diagnoses were made: posthepatitic cirrhosis with hepatic insufficiency (clinical); E. coli septicemia (clinical); ascites (5000 cc.); jaundice, severe; hypertrophy of spleen (184 gm.; normal, 66 gm.); hypertrophy of kidneys (290 gm.; normal, 140 gm.), with tubular degeneration; varices of esophagus; ulcerative esophagitis; edema and ecchymoses of small and large intestines; edema and hemorrhage of lungs; hemorrhage of urinary bladder.

Comment

As in patients with other serious and debilitating diseases, patients with severe disease of the liver may be more susceptible to bacteremia. The filtering action of the reticuloendothelium of the liver [5] is considered to be one of the defenses against infection. The loss of such a defense has been said to be a factor in the occurrence of bacteremia in patients with severe hepatic disease.[2]

Various investigators * have reported on the circulatory changes in cirrhosis of the liver. More recently, Mann, Wakim, and Baggenstoss [8] studied the circulation of the human liver and showed that, unlike that of the normal liver, anastomoses of fair size between the portal and hepatic veins are found fairly commonly in cases of cirrhosis. Popper and associates [7] described these anastomoses as constituting a circulatory disadvantage to the liver, in that blood is shunted past it from the portal to the hepatic veins. These anastomoses, theoretically, could serve as a bypass, so that bacteria entering the portal circulation from the intestines, as is said to occur,[2] could pass to the general circulation without being exposed to the reticuloendothelium of the liver (Kupffer cells). In addition to these intrahepatic shunts, blood from the intestinal tract may completely bypass the liver in cirrhosis by way of the numerous collateral pathways outlined so well by McIndoe.[9]

Schatten and co-workers [10] cultured blood from the portal vein of 25 patients at laparotomy and obtained positive results in 32%. Culture of blood taken simultaneously from a vein in the arm gave negative results in every instance. These results seem to corroborate the hypothesis that bacteria enter the portal circulation from the intestines and might explain the occasional association of bacteremia with severe disease of the liver.

Also, it is conceivable that the changes in protein content of the blood in the cirrhotic patient may be accompanied by a defect in immunologic mechanisms.

One should be aware of this complication in the patient with severe hepatic disease, and, in the event of fever not explained otherwise, the blood should be cultured repeatedly. Treatment of the bacteremia, when it complicates severe disease of the liver, is not satisfactory, however.

Summary

The occasional association of severe disease of the liver with bacteremia due to Gram-negative bacilli seems more than coincidental. Four illustrative cases are presented. In patients with severe disease of the liver who have fever not explained otherwise, the blood should be cultured repeatedly. The complication is apparently of evil omen, since the infection appeared to be eradicated by antibiotic therapy in three of our four patients, yet all four shortly died.

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Renal Osteodystrophy in Adults

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Renal osteodystrophy may be defined as bone disease caused by chronic renal insufficiency. The skeletal changes may include osteomalacia, osteoporosis, and osteosclerosis or a combination of these. The changes may also be identical with those of osteitis fibrosa generalisata due to hyperparathyroidism.

In this short paper we are not concerned with the mechanism of production of the osteodystrophy, which appears to be as yet ill-understood, but rather with the remarkably constant clinical picture shown by the three cases presented here. It is to emphasize that in the short period of six months we have seen three new cases, although the disease is usually considered to be rare, and to indicate the value of bone biopsy that we present this report. It seems quite likely that many cases of renal osteodystrophy in adults are overlooked and that minor or moderate degrees of the condition are commoner than is generally supposed.

In a comparatively recent historical review by Swart (1930) it is noticeable that all the patients were children or young persons. Probably the reason for this bias at that time was largely that the first described case was in a child (Morley-Fletcher, 1911). The deformities produced in the growing child are more obvious than the insidious and chronic changes in the adult.

Ginzler and Jaffé (1941) have shown that varying degrees of bone disease are to be found regularly in adults dying after prolonged renal insufficiency. More recently, Follis and Jackson (1943) studied vertebral bone changes in 39 autopsy cases of adults with chronic renal failure and found that osteomalacia or osteosclerosis was present in most of them. Such frequent abnormalities were also reported in 1935 by Rutishauser.

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Report of Cases

CASE 1.—A 49-year-old woman was admitted on June 26, 1954. She gave a history of 10 years of aching pains in the thighs, worse on walking and responsible for several falls. She complained also of nagging pains in the chest wall and lumbosacral area. For two years she had had swelling of the ankles, partly controlled by mercurial diuretics. She had suffered from exertional dyspnea for 12 months. Nocturnal frequency of micturition was admitted on direct questioning. Her general health had been poor for some years, although she had a good appetite, and except for occasional abdominal pains and nausea there were no other definite symptoms. There was a history of toxemia of pregnancy at the age of 21 years.

Examination.—The patient was thin and pale, with a sallow complexion. Scattered ecchymoses were present on the arms and legs, and there was minimal ankle edema. The remaining physical signs were a moderate kyphoscoliosis, tenderness of the ribs, thickened peripheral arteries, and a blood pressure of 200/80. Bone disease was suspected because of the widespread pains. Radiographs of the skull, spine, and pelvis were abnormal, and so further investigations were undertaken to determine the cause.

Radiological Appearances.—The skull showed a widespread woolly appearance, with numerous small areas of rarefaction. The pelvis showed fractures of both pubic bones and ascending ramus of the left ischium (Figs. 1 and 2). Ill-defined trabeculation and some woolly changes could be seen in the kyphoscoliotic spine. There were a number of healed fractures of the ribs. The phalanges showed porosis and early subperiosteal bone resorption. All the bones showed some degree of generalised porosis.

Fig. 1 (Case 1).—The radiological appearance of the skull, showing numerous small areas of rarefaction and the woolly appearance.

Fig. 2 (Case 1).—Radiological appearance, showing fractures of both pubic bones and the ascending ramus of the left ischium. Some degree of generalized porosis is also present.

Bone Biopsy.—The report on the tibial bone specimen was as follows: "There is more than normal osteoclastic expansion of the Haversian canals with a little fibrosis, and this is associated with the deposition of narrow seams of osteoid. The changes may indicate a moderate degree of renal osteodystrophy but are minimal and imply little more than an accelerated turn-over of bone."

Urine.—A moderate cloud of albumin was present, but there were no cells or casts, and culture was sterile. The maximum urine specific gravity was 1.010.

Blood.—Hb., 10.8 gm. per 100 cc. RBC, 3,200,000 per cu. mm. White cells, 7000 per cu. mm. Film showed macrocytic normochromic red cells with occasional microcytes. Later values were Hb., 10.0 gm. and 9.1 gm. per 100 cc.; WBC, 5800 and 5000 per cu. mm. Marrow examination showed erythron hypoplasia and macronormoblasts but no other abnormality.

The erythrocyte sedimentation rate (ESR) ranged from 36 to 66 mm. in the first hour (Westergren).

Blood urea levels at various times were: 54, 43, 44, 59, 78, and 85 mg. per 100 cc., showing a gradual rise as time went on.

Alkali reserve was 18 and 19 mEq. per liter; serum calcium, 6.4, 8.9, 8.2, 7.3, and 6.7 mg. per 100 cc.; serum alkaline phosphatase, 19, 27, 6.3, and 6.1 K.A. units; serum inorganic phosphorus, 5.1, 5.5, and 6.7 mg. per 100 cc.

The serum proteins fell from a level of 7.7 gm. to 4.8 gm. per 100 cc. during the eight months of observation. The albumin-globulin ratio was at first 4.6:3.1 and later 2.8:2.0.

Treatment and Progress.—Calciferol, 50,000 units daily, with sodium citrate, 2 gm. daily, and calcium lactate, 3 gm. daily, gradually reduced bone pain in the period of one month. However, the patient's general condition deteriorated, with rising blood pressure (260/100), increasing edema and hypoproteinemia, rising blood urea, and other features of progressive renal failure, including severe exertional dyspnea. She died at home of "uremia" in March, 1955, and autopsy was not performed.

Case 2.—A 64-year-old man was admitted on Aug. 10, 1954. He gave an indefinite history of rheumatic-like pains which had been present for 18 months in the legs, sacrum, and ribs, made worse by exertion. He had occasional nausea and dizziness, an unpleasant taste in the mouth, and an irritating nonproductive cough. He had lost some weight. There were no urinary symptoms and no history of renal disease.

Examination.—He was a dull rather drowsy man, slow in speech and action. There was a dusky brown pigmentation of the face and a noticeable dryness of the tongue and skin. The blood pressure was 190/90, and the peripheral arteries were thickened. No other significant abnormality was found. The similarity of the clinical picture to that of Case 1 lead to the suspicion of bone disease.

Radiological Appearances.—The lumbar spine showed areas of osteosclerosis, and the pelvic bones, indistinct and sparse trabeculae. Calcification of the prostate, spermatic cords, and iliac arteries was observed. There were also some calcified deposits below the left sacroiliac joint. Fusion of both sacroiliac joints was present and was thought to be due to old ankylosing spondylitis. The skull was normal in appearance. There was some irregularity of the borders of the phalanges but no definite subperiosteal bone resorption. No fractures or pseudofractures were seen. The appearances described above were not considered diagnostic of generalized bone disease.

Bone Biopsy.—The histological report on the right tibial bone specimen was as follows: "Changes are present in this shaft bone, though

not marked. The Haversian canals are generally widened and some are the seat of osteoclastic resorption activity, but there is no generalized osteitis fibrosa. Narrow osteoid seams are present here and there. The general picture however, is one of osteoporosis predominating over osteomalacia."

Urine.—There was a variable cloud of albumin in most specimens, but on two occasions it was absent. There was no cellular deposit, and culture was sterile. Maximum urine specific gravity was 1.008.

Blood.—Hemoglobin, 12.6 gm. per 100 cc., gradually falling to 10.7 gm. per 100 cc. in four months. RBC fell from 3,600,000, to 3,500,000 per cu. mm. in the same period. White cells varied from 3000 to 7000 per cc. mm., with a normal differential count. Blood film showed macrocytic normochromic red cells. Bone marrow examination showed normoblastic red cell series.

The ESR was 33 mm. in the first hour (Westergren). Blood urea was 84, 104, 79, and 72 mg. per 100 cc. Alkali reserve was 22 and 21 mEq. per liter; serum inorganic phosphorous levels, 5.6 and 5.3 mg. per 100 cc.; alkaline phosphatase, 33, 31, and 35 K.A. units; serum albumin, 5.2 gm., and serum globulin, 1.7 gm. per 100 cc.

An intravenous pyelogram showed no concentration of dye.

Treatment and Progress.—No marked changes were observed during the eight months of observation. Pain was relieved temporarily by codeine tablets but was still complained of in April, 1955. It was decided to avoid calcium and calciferol therapy in order to further observe the natural history of the disease in this patient and also in view of the possibility that this treatment might produce more renal damage.

CASE 3.—A 38-year-old woman was admitted on Feb. 10, 1954. She complained of aching pains in the lower lumbar region, present for the last four years. Stiffness in the right thigh had caused difficulty in walking for two years. A past history of anemia and "pyelitis" of two years standing was given. These two conditions had not responded adequately to treatment. Questioning elicited the symptom of rather vague generalized hyperesthesia for one year as well as a poor appetite and some increased frequency of micturition.

Examination.—She was a pale thin woman with spontaneous carpal spasms. There was tenderness over the lumbar spine and in the thighs on deep pressure. Muscular power was generally poor, especially in the legs, although in the latter this was partly due to muscular pain. The blood pressure was 138/88. No other significant physical signs were found.

Radiological Appearances.—The dorsolumbar spine had an amorphous woolly appearance, and normal trabeculation was not present. The hands showed early subperiosteal bone resorption of the phalanges and localized round areas of rarefaction in the cortex and medulla of the metacarpals (Fig. 3). The ribs were diffusely altered in "texture."

Fig. 3 (Case 3).—The appearance of the hands; (*a*) localized rounded areas of rarefaction in the first, fourth, and fifth metacarpals; (*b*) generalized loss of normal trabeculation; (*c*) early subperiosteal bone resorption.

A pseudofracture was present in the left scapula. The cortex and medulla of one tibia showed slight loss of distinction.

Biopsy of bone was not carried out in this case.

Urine.—A large quantity of albumin was constantly present, and there were many leucocytes. A coliform bacillus was cultured.

The maximum concentration and dilution of the urine were specific gravity 1.006 and 1.001.

Blood.—Hemoglobin was 59%, i.e., 8.9 gm. per 100 cc. RBC count was 3,000,000 per cu. mm.; white cells, 7000 per cu. mm. Blood film showed a macrocytic normochromic red cell picture.

After intramuscular iron therapy the hemoglobin levels recorded were 62% and 63%, no response having been produced.

Blood urea levels were 126, 126, 164, 188, and 172 mg. per 100 cc.; urea-clearance test was 10% to 12% of average normal; serum alkali reserve,

19, 15, and 23 mEq. per liter; serum alkaline phosphatase, 51 K.A. units; serum calcium, 5.8, 3.8, 4.4, 5.3, 5.1, and 5.5 mg. per 100 cc.; serum proteins, 6.5 and 7.6 gm. per 100 cc.

The erythrocyte sedimentation rate was 32 mm. in the first hour (Westergren).

Treatment and Progress.—Chronic renal failure progressed to a fatal conclusion three months after the first admission. Bone pain was moderately improved by the daily administration of the following therapy: calciferol, 100,000 units; calcium gluconate, 36 grains (2.16 gm.), and sodium citrate, 3 gm. Back pain was made less severe by the use of a spinal support. The patient died at home, and an autopsy was not performed.

Disease Incidence and Bone Histology.—Ginzler and Jaffé (1941) described 12 cases of chronic renal insufficiency in which histological studies of bone were made after autopsy. Nearly all showed changes of some degree, often mild but occasionally advanced. The bones appeared normal to the naked eye in the mild case, but sections showed scattered resorption lacunae on the surfaces of the spongy trabeculae and on the walls of the vascular canals. There was no significant new bone formation.

In more advanced cases there was perforation of the trabeculae by tracts of connective tissue and the cortical bone showed erosion and enlargement of the Haversian canals. There was some reparative change consisting of new bone side by side with the other changes, but the tendency was still to porosis.

In the most advanced degree of change the spongiosa was close-meshed and the trabeculae were thick and distorted by accretion of new bone.

Clinical methods, apart from bone biopsy, might fail to detect minor and moderate changes of renal osteodystrophy. This certainly applies to our Case 2, in which radiological signs were not in the least diagnostic. Albright (1949) considered that this bone disease was histologically identical with osteitis fibrosa generalisata and ascribed it to secondary hyperparathyroidism. In 1949 he accepted chronic acidosis as the most probable cause of the bone lesions. There was no osteitis fibrosa in our two bone biopsies. They showed increased osteoclastic expansion of Haversian canals and narrow osteoid seams. In Case 1 the changes were of minor degree in the left tibial biopsy despite fractures of ribs and pelvis and other gross radiological changes, especially in the skull. In Case 2 osteoporosis and osteomalacia were more marked, although radiology revealed only minimal and indefinite abnormalities.

Follis and Jackson (1943) noted osteoporosis and osteomalacia in their cases. They also reexamined the published photomicrographs of the case reported by Albright, Drake, and Sulkovitch (1937) and stated that in fact the osteoid seams were abnormally wide. Snapper (1943) also noted this feature. In the cases he reviewed, some showed osteoporosis and others osteitis fibrosa. Although this condition is thought to be a rare disease by most writers on the subject, the autopsy studies indicate otherwise. The incidence in adults of symptomatic renal osteodystrophy is not known.

Radiological Appearances.—Albright mentions generalized decalcification of the skeleton and a ground-glass appearance of the skull similar to that seen in hyperparathyroidism. Swart (1930) also noted the fuzzy appearance of the skull, which he likened to Paget's disease of bone. Generalized bone atrophy and softening were present in children. Norman, Perlman, and Bastable (1947) saw circular defects in the parietal bone and similar areas in other bones. There was subperiosteal bone resorption in the phalanges. Recently, Crawford and coworkers (1954) emphasized the feature of osteosclerosis. Soffer and Cohn (1943) remark on the mottling of the skull, diffuse generalized osteoporosis, and areas of rarefaction. Occasionally, fairly large cysts are seen. One of their cases had one in the middle of the left clavicle.

Of our cases, two showed generalized rarefaction of bones and other changes, which included a woolly appearance of the skull, presumed to represent osteosclerosis,

with areas of rarefaction; fractures and a pseudofracture; ill-defined trabeculation and a woolly appearance in the spine; early subperiosteal bone resorption in the phalanges, and cystic changes. There were no large cysts. Case 2 was more difficult to assess, some sclerotic changes in the vertebra and sparsity of trabeculation being all that was seen.

Metastatic Calcification and Mönckeberg's Sclerosis.—Most authors mention these two features. Our three cases had clinically obvious Mönckeberg sclerosis. Metastatic calcification was not a feature in Cases 1 and 3, but Case 2 had some calcification in the pelvic cavity, spermatic cords, and prostate; however, these changes could be coincidental.

Clinical Features.—Bone Pain: The presenting symptom in the three cases was bone pain. Both women were considerably incapacitated by it, particularly in the spine, pelvis, and legs. It was aggravated by sitting and walking. One had had pains for 4 years, and the other, for 10. The latter had an obvious limp. Simple tests of renal function seem to be called for in such cases, to avoid missing early renal osteodystrophy.

Renal Insufficiency: Two of the cases gave no history which would bring to mind at once the thought of chronic renal disease. The other had a history of two years of pyelonephritis, although it seems likely that it may have been of longer duration, in view of the bone lesions. In Cases 1 and 2 urinary symptoms were noticeably absent, but the symptoms of poor appetite, general ill-health, vague abdominal pains, pallor, dry mouth, and mental hebetude were no doubt caused by chronic uremia. In spite of the absence of specific symptoms, renal insufficiency was shown clearly by the relevant tests.

Urine concentration was poor, and the specific gravity was relatively fixed. Albuminuria was nearly always present, but one or two negative results in a fair number of tests have warned us that a single test may be misleading. Case 3 had infected urine, but in Cases 1 and 2 it was sterile and without cellular deposit.

The blood urea was raised in each case, but some levels recorded were borderline. Severely uremic persons are unlikely to live long enough to develop bone lesions, although the diagnosis may not be made until the final stages of renal failure have been reached.

The serum inorganic phosphate level was elevated in the three cases, though only moderately so. Even a slight rise above normal would appear to be quite significant, and Case 1 showed an increasingly higher level as renal insufficiency advanced. Snapper mentions cases of renal osteodystrophy in North China in which hyperphosphatemia was absent. This may have been due to a low phosphate intake. Acidosis was, however, invariably present in these cases. Hypoproteinemia may be produced by protein loss due to albuminuria, as in Case 1.

Acidosis was moderate in degree but constantly present. It is considered by Rutishauser and Jaffé (1935) to be the basic biochemical lesion which, if chronic, may lead to renal osteodystrophy. These authors produced bone changes in dogs by feeding with ammonium chloride. As with the other vital biochemical changes, acidosis is not likely to be severe until the late stages of the disease. Almost all untreated uremics are acidotic (Relman, 1954).

Other Biochemical Changes.—Serum alkaline phosphate: We note that this was variable and sometimes within normal limits, as in two recorded levels in Case 1. The other two cases had clearly elevated levels at all times.

The serum calcium was low in all three cases.

It is to be noted that many cases of chronic renal insufficiency have hyperphosphatemia and hypocalcemia but that these are not in themselves in any way diagnostic of bone disease. On the other hand, a rise in alkaline phosphatase in renal

cases is an indication that bone changes are occurring.

The erythrocyte sedimentation rate was raised in each case.

Differential Diagnosis.—This resolves itself mainly into a consideration of conditions which combine bone disease and chronic renal failure. Primary hyperparathyroidism may be radiologically indistinguishable from renal osteodystrophy, and thus differentiation may depend on bone histology. Although Albright (1937) considered that the histological changes of both renal osteodystrophy and osteitis fibrosa generalisata due to primary hyperparathyroidism were identical, the changes found in our cases were quite unlike those of the latter disease. The diagnosis of primary hyperparathyroidism is made difficult if secondary renal failure results from renal calcification, but hypocalcemia of the degree seen in the present cases is of late occurrence. There was no demonstrable renal calcification or nephrolithiasis in our cases.

In myelomatosis the radiological changes in the affected bones may be those of rarefaction or decalcification and not the commoner "punched-out" lesions. The skull roentgenograms in Case 1 were certainly reminiscent of myelomatosis apart from the "woolly" appearance. These areas, presumed "osteosclerotic," were seen also in Case 3 and favor the diagnosis of renal osteodystrophy. Subperiosteal bone resorption does not occur in myelomatosis, although it is perhaps a possibility in the rare case of secondary hyperparathyroidism in this disease. Renal failure is common in myelomatosis, though usually late in the disease and accompanied by the usual manifestations such as Bence Jones proteinuria, hyperglobulinemia, and typical marrow smears. There was no evidence of carcinomatosis, and, in fact, the radiological features were unchanged after months. Advancing renal failure was present in the two fatal cases, and it is reasonably certain that the deaths were due to "uremia."

The mixture of osteoporosis and osteomalacia in Case 2 and the "accelerated turn-over of bone" in Case 1 could not be accounted for by any other explanation than the renal failure, and the roentgenograms did not have the appearance of simple osteoporosis or osteomalacia, nor was any cause of the latter conditions suggested by the histories or clinical pictures. In any case, the hypocalcemia and phosphate retention is against such diagnosis unless coincident renal disease were postulated.

Treatment and Progress.—Cases 1 and 3 are both dead of renal failure. Case 2 is unchanged at the time of writing, and his pains have not abated. Although calciferol, calcium, and sodium citrate relieved pain in Cases 1 and 3, there was a rather rapid worsening of the "uremia." We do not know whether the treatment could have been partly responsible for this or whether it was inevitable in these two patients. Therapy produced no detectable radiological improvement during the period of observation.

Summary

Three cases of chronic uremia with bone changes are presented. The outstanding symptom of bone pain and the other clinical features are described. Tibial bone biopsy was used in two cases and proved the presence of generalized bone disease, although the histological features shown are not necessarily representative of other parts of the skeleton. Gross local changes were evident radiologically in one case in spite of only minimal histological changes in the biopsy specimen.

Dr. H. P. Brody gave permission to publish the above cases, and Dr. E. K. Blackburn, Professor Collins, Professor Jepson, Dr. Jordan, and Dr. J. Wilkie helped in this study. Mr. Coombes, Radiological Department, Royal Infirmary, Sheffield, contributed the photographic reproductions.

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Evaluation of the Hemostatic Properties of Synthetic Serotonin

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With the Technical Assistance of Nancy Martino, A.S., and Rose Mele, MT (ASCP)

Introduction

Serotonin (5-hydroxytryptamine) creatinine sulfate (5-HT), a constituent of serum and platelets, has many and complex biologic functions. Some of these are connected with the mechanism of hemostasis. Thus, it is thought by many, although not proved,[1] that serotonin may induce the vasoconstriction which is seen to follow vascular injury.* Also, it has been found that the parenteral administration[4] or local application[5] of the drug reduces bleeding time in rabbits, while its intravenous administration[5] is stated to increase the capillary resistance in guinea pigs. Recent experiments have postulated a role of serotonin in the retraction of the clot,[5] a finding which has not been confirmed.[7] On the other hand, serotonin is entirely inactive in the mechanism of blood coagulation.[4]

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* References 2 and 3.

Allegri and Ferrari[8] have recently reported control of clinical bleeding, shortening of the bleeding time, and increased capillary resistance (as judged by the results of the tourniquet test) after parenteral administration of serotonin to a few patients with primary or secondary thrombocytopenic purpura. Favorable results have also been reported in anaphlactoid purpura and in idiopathic menorrhagia.[9] In view of the need for an effective readily available hemostatic agent in many hemorrhagic diseases, it was felt that extension of these studies to a larger number of patients with various hemostatic abnormalities would be worth while.

Materials and Methods

Crystalline serotonin creatinine sulfate was made available by Dr. Joseph Webb, of the Upjohn Company, Kalamazoo, Mich. For intravenous administration, the desired weight of the drug was dissolved in 5% dextrose solution; for intramuscular use, the drug was dissolved in saline solution, immediately prior to use. Bleeding time was studied by the method of Ivy,[10] and whole blood clotting time, by the procedure previously described, with use of silicone-coated test tubes.[11] Techniques for the study of capillary fragility (tourniquet test), clot retraction, and prothrombin consumption have been previously published[12]; platelets were counted by a modification[12] of our direct method.[13]

A total of 22 patients were studied. Seven were normal. Since there is no question that serotonin is ineffective on the coagulation mechanism, the patients studied (15) were suffering either from primary vascular defect (5) or from various forms of thrombocytopenia (10).

Results

(1) Effect of Serotonin on the Hemostatic Mechanism in Normal Subjects

Seven healthy persons received intravenous infusion of 0.4 mg/kg. of serotonin

creatinine sulfate in 250 ml. 5% dextrose solution over a period of several hours. Slowly flowing infusion (40 drops/minute) in four subjects caused significant reduction of the bleeding time (determined with the method of Ivy) (Table 1). There were no appreciable effects on the platelet count or the rate and the degree of clot retraction. Blood clotting time was also unmodified. Faster rate of injection (80 to 100 drops/minute) in three subjects did not affect the degree of reduction of the bleed-

period, daily for four days. The third one received intramuscularly 0.25 mg. serotonin per kilogram in saline solution twice a day for a period of two weeks. None of the patients experienced rise in platelet count or improvement in clinical bleeding or laboratory findings (clot retraction, bleeding time, tourniquet test, and prothrombin utilization during clotting). It was observed, however, that intramuscular injections in one patient were followed during the first three days by oozing and formation of hematoma at the site of puncture. This no longer occurred after the third day. This

TABLE 1.—*Effect of Intravenous Serotonin on the Bleeding Time of Normal Subjects, Determined by Ivy's Technique*

Time, min.	0	15	30	60	120	150	180	240	360
Serotonin, mg.*	----	3	6	12	24	----	----	----	----
				Bleeding Time, Min.					
Subject 1	5½	5	2½	1	1½	3½	4	6½	----
Subject 2	4	1½	1	1	1½	4	4	4½	----
Subject 3	4½	3½	1½	2	2	4½	4	----	----
Subject 4	6	5	2½	2½	2½	3	4½	6½	5½

* These figures represent the total amount of Serotonin administered at any given time during the study. Administration was discontinued at 120 minutes.

ing time. This did not occur until a minimum of 3 to 6 mg. of serotonin had been administered. The effect was also very fleeting, the bleeding time returning to pretreatment values within 15 minutes to 2 hours after suspension of the injection.

(2) Effect of Serotonin on the Hemostatic Mechanism in Thrombocytopenia

Ten patients were studied. Three cases were instances of untreated thrombocytopenic purpura of the idiopathic variety, chronic in type. There was moderate skin and mucosal bleeding; laboratory findings typical of platelet deficiency (poor clot retraction, positive tourniquet test, prolonged bleeding time, poor prothrombin utilization during clotting) were present in all instances. Two patients received intravenously 0.5 mg. of serotonin per kilogram in 5% dextrose solution over an eight-hour observation could be interpreted as evidence of favorable, although aspecific, effect of serotonin on bleeding manifestations.

Seven patients with the secondary type of thrombocytopenia composed the second group. Three suffered from acute leukemia of various types: two, from aplastic anemia; one, from reticulum-cell sarcoma, and one, from Hodgkin's sarcoma with hypersplenism. All were untreated at the time of study, had moderate to severe skin and mucosal bleeding, and showed laboratory findings compatible with marked thrombocytopenia. All patients first received intravenous injections of 0.5 mg/kg. of serotonin in 5% dextrose over a four-hour period for two consecutive days. Subsequently, the drug was administered intramuscularly in doses of 0.1 mg/kg. in saline solution at four-hour intervals for

four to seven days. In this group, also, there was no significant improvement in bleeding manifestations. Abnormal platelet count, bleeding time, tourniquet test, and prothrombin utilization remained unmodified.

(3) Effect of Serotonin on the Hemostatic Mechanism in Patients with Vascular Pseudohemophilia (Table 2)

We define as vascular pseudohemophilia a hemorrhagic diathesis characterized by prolonged bleeding time and slightly increased capillary fragility. In this disease platelets have adequate number and function and blood coagulation process is normal.[12] In four, two received intravenously 0.6 mg. of serotonin per kilogram over a four-hour period; the other two received intramuscularly 0.2 mg/kg. every six hours for three days. Intravenous administration of the drug was followed by temporary reduction in the bleeding time. Protracted intramuscular administration had erratic and fleeting effects (Figure). Clot retraction, platelet count, and prothrombin utilization during clotting remained unmodified. The patient with active bleeding received intravenously 0.3 mg/kg/hour of serotonin in 5% dextrose, for a total of 25 mg. over a 12-hour period. The bleeding time was reduced from 18 to 7 minutes, but there was only mild effect on the bleeding manifestations.

TABLE 2.—*Effect of Intravenous Serotonin on the Bleeding Time of Patients with Vascular Pseudohemophilia*

Time, min.	0	60	120	280	240	360	480
Serotonin, mg.*	0	5	10	15	20		
			Bleeding Time, Min.				
Patient 1	19	10½	7½	5	5½	14	21
Patient 2	14	6	6½	4½	7½	9	12

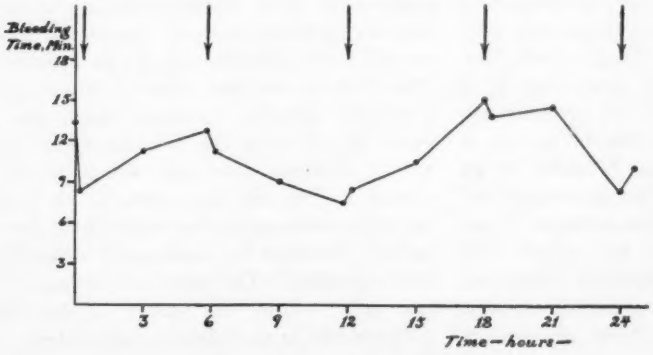
* These figures represent the total amount of Serotonin administered at any given time during the study. Administration was discontinued at 240 minutes.

ability of the metarteriole to contract following injury may be responsible for the bleeding manifestations, which are seldom spontaneous, commonly following traumatic or surgical injury.

Five such patients were given serotonin: four did not present bleeding at the time of study; in one there was profuse oozing following dental extraction. Of the group

Side-Effects of Therapy with Serotonin

In three of four cases rapid intravenous administration of the drug (approximately 0.5 mg/minute) was followed by severe



Effect of intramuscularly administered serotonin on the bleeding time in vascular pseudohemophilia. The patient received 0.2 mg/kg. of serotonin intramuscularly every six hours (arrow). Bleeding time was determined by method of Ivy.

burning pain along the course of the vein for a distance of 5 to 7 in. (12.5 to 17.5 cm.) from the point of injection. In two of four cases increase in local venous pressure [14] caused reflux of blood into the afferent tube. One patient fell deeply asleep at the end of the intravenous infusion, being aroused with difficulty one hour later. The same patient developed generalized urticaria 10 hours later, lasting 24 hours. A few of the patients receiving the drug intravenously felt flushed and nervous during and for a few minutes after suspension of the infusion.

Comment

The striking effect of serotonin on the bleeding time in experimental animals has been considered as primary evidence of the role of this substance in hemostasis and might prompt its use in the management of hemorrhagic disorders. While the effect of serotonin on the bleeding time may represent nothing more than a facet of its vasoconstrictor effect on the capillary vessel,[1] the evaluation of the effectiveness of serotonin in the management of hemorrhagic disorders meets two important obstacles, which have been encountered previously in the evaluation of antihemorrhagic agents. Often, no laboratory tests are available to "measure" the effect of such drugs. Even when such methods are available, there may be poor correlation between laboratory results and clinical observations. One then relies heavily on the careful clinical study of the patient, thereby encountering the second obstacle, the unpredictability of bleeding manifestations in patients with hemorrhagic disorders. Thus, satisfactory therapeutic results of a new drug in a case of acute idiopathic thrombocytopenic purpura could easily be due to its use at a time when the disease is about to go into spontaneous clinical or hematologic remission. This might have occurred in one of the cases reported by Allegri and Ferrari.[8] It is not surprising, therefore, that the evaluation of an antihemorrhagic drug will vary greatly from observer to observer, until time and extension of studies finally determine the real value of its clinical use.

We have not been impressed by the hemostatic properties of serotonin in various hemostatic disorders. A. No significant improvement of bleeding manifestations or reduction in the bleeding time was seen in thrombocytopenic patients. It would appear that synthetic serotonin does not represent the factor in platelets which controls behavior of the bleeding time. Moreover, serotonin appeared unable to reduce the bleeding time in the absence of circulating platelets. B. Reduction of bleeding time in vascular pseudohemophilia was significant but too temporary to be of any practical value. An interesting finding was the lack of beneficial effect on hemorrhage in a patient whose bleeding time (Ivy) was reduced by serotonin. This observation might be explained if one remembers that the vasoconstrictor effect of serotonin may vary greatly from vascular district to district.[1] Thus, serotonin might have failed to induce vasoconstriction at the site of clinical hemorrhage, while still affecting the bleeding time favorably.

As mentioned already, serotonin shortened the bleeding time only in subjects with a normal number of platelets. Like epinephrine and arterenol,[15] antifibrinolysin,[16] etc., serotonin may be carried by platelets rather than represent one of their intimate constituents. It is then possible that the absence of platelets may prevent the transport of serotonin to the site of activity. This hypothesis we tried to demonstrate experimentally, without success. Serotonin was incubated with platelet-rich plasma in vitro. The mixture was then injected into a patient with secondary thrombocytopenic purpura; no effect on the bleeding time was noted. Perhaps serotonin, which is absorbed by normal dog platelets,[17] is not taken up by human platelets which have been partially damaged by processes of collection and separation. The previous findings, in any case, indicate the futility of the use of serotonin in thrombocytopenic states.

Summary

Repeated administration of synthetic serotonin (5-hydroxytryptamine) intravenously or intramuscularly failed to shorten the bleeding time or to correct the poor retraction of the clot in patients with thrombocytopenia. It fleetingly reduced the prolonged bleeding time in patients with vascular pseudohemophilia.

The drug failed to improve the bleeding tendency in thrombocytopenic states. Hemorrhage continued in one case of vascular pseudohemophilia, although the bleeding time was corrected to almost normal values by administration of the drug.

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Carbohydrate Metabolism

II. Changes in the Serum Pyruvic Acid During Glucose-Tolerance Test in Normals, Diabetics, and Prediabetic Women

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The present knowledge of intermediary metabolism is still incomplete; yet of the few well-established facts it is generally accepted that pyruvic acid is one of the most active intermediary compounds of living cells. Pyruvic acid participates prominently in the transformation of the three classes of foodstuffs: in the oxidation of carbohydrate as the terminus of the Embden-Meyerhof scheme of anaerobic glycolysis; in the introduction of protein to the tricarboxylic acid cycle through chemical interrelationships with alanine, and in the metabolic changes of fat through a 2-carbon acetyl compound similar to acetic acid. Pyruvic acid is truly a "hub toward which converge carbohydrate, fat and protein in their catabolic and anabolic reactions" (Barron).

Since the early 1940's a sizable body of literature has appeared in regard to the role of pyruvic acid in the chemistry of biologic reactions. Thus blood pyruvate has been found elevated in decompensated cirrhosis, thiamine deficiency, malnutrition, hepatic coma, congestive heart failure, periods of fever, physical exercise, and large infusions of glucose.* Since phosphorylated thiamine must be present for the complete utilization of pyruvic acid, in many of these conditions where pyruvic acid is elevated a thiamine deficiency exists, frequently secondary to diminished phosphorylation activity in the liver.

Of particular interest has been the response of pyruvic acid to loading of the organism with glucose. Unfortunately, although most of the work on this subject has been intensive and meticulous, the results have frequently been inconclusive, equivocal, or mutually contradictory. Among the earliest reports, Bueding observed a significant rise in the blood pyruvic acid after glucose administration in normal subjects, but in patients with diabetes mellitus the rise was either absent or delayed. Following preparation with insulin, however, the diabetics showed the normal rise in pyruvate. Working with normal and depancreatized dogs, the same author noted similar findings when glucose was given intravenously. He furthermore demonstrated that the rate of removal of pyruvic acid was the same in normals and diabetics; hence it was concluded that insulin probably increases the formation of pyruvate rather than retards its removal.[5]

Klein, in 1943, reported a significant though delayed rise in blood pyruvic acid following glucose taken orally in diabetics.[6] Horwitt, Hills, and Kreisler observed a similar delayed rise in patients with diabetes mellitus, and they proposed this phenomenon as a test for mild diabetes. They furthermore noted that exercise eliminated the delayed rise in diabetics and resulted in a prompt elevation of pyruvate, as with normals.[7] In this they confirmed the previous work of Himwich and Himwich.[8] Horwitt and co-workers [7] found insulin to exert no

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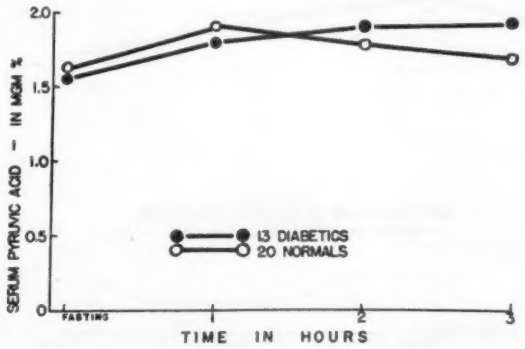
* References 1-4.

influence on blood pyruvate levels in diabetics who were exercised, and it was concluded that insulin is not necessary to convert carbohydrate to lactic and pyruvic acids during exercise.

Miller administered dextrose (D-glucose) intravenously to three humans with diabetes and saw no appreciable rise in blood pyruvic acid; however, after insulin was given the normal prompt elevation of pyruvate occurred.[9] Root, Stotz, and Carpenter, employed the intravenous glucose-tolerance test observed no rise in pyruvic acid in 18 of 20 severe diabetics, while 2 of 4 mild diabetics exhibited a normal rise.[10] Amatuzio, Shrifter, Stutzman, and Nesbitt employed the intravenous glucose-tolerance test and noted a minimal and delayed elevation of blood pyruvate in mild diabetics, while in patients with severe diabetes the pyruvic acid dropped at 30 minutes and continued to rise slowly throughout the remainder of the procedure.[11]

It was our intention to clarify this somewhat confused picture by studying the differences in pyruvic acid response incident to route of administered glucose. Furthermore, a unique group of subjects was available. These were women who had delivered a baby weighing 10 lb. (4535 gm.) or more. Kritzer [12] reported that 31% of these show a typical diabetic configuration to the glucose-tolerance curve on an average of two and one-half years after delivery. The remainder, although exhibiting normal carbohydrate metabolism now, can be presumed to yield a certain percentage of frank diabetics, and so they are termed "prediabetics." To learn whether certain metabolic abnormalities appeared before the defect in carbohydrate utilization became apparent, the blood pyruvic acid and serum inorganic phosphate were studied. The latter study is reported elsewhere.[13]

The studies were carried out on 20 normal young women, 13 elderly patients with long-standing mild diabetes who required no insulin, 30 prediabetics as defined above, and 16 women who had given birth to large babies but now showed a diabetic oral glucose-tolerance curve (designated "recent diabetics"). The standard oral glucose-tolerance test was carried out on these subjects, and the Thorn intravenous glucose-tolerance test was used with nine normals and eight elderly persons with mild diabetes.[14] The daily dietary intake of all subjects had included at least 300 gm. carbohydrate for 72 hours prior to testing, and all persons were at a basal state.



MEAN SERUM PYRUVIC ACID DURING ORAL GLUCOSE TOLERANCE TEST

Figure 1

Blood samples were uniformly handled by precipitation with trichloroacetic acid immediately following venipuncture, and subsequent pyruvate determinations were performed within two hours. Pyruvic acid was determined by the method of Lu,[15] while the Benedict method [16] was used for blood sugar.

Results

Following the oral administration of glucose the 20 normal subjects in the control group showed a moderate rise of blood

pyruvic acid at the one-hour level, with a gradual decline to a near normal value at the end of three hours, the mean values being 1.63, 1.90, 1.79, and 1.69 mg. per 100 cc. (Table 1 and Fig. 1). The average values for blood pyruvate during the oral glucose-tolerance test in 13 patients with mild diabetes rose gradually, paralleling the behavior of the blood glucose, specifically, 1.55, 1.80, 1.90, and 1.91 mg. per 100 cc. (Table 1 and Fig. 1). Figure 2 discloses a blood pyruvic acid response similar to the control group in 30 prediabetic women whose glucose consumption is still normal during an oral glucose-tolerance test, the pyruvate levels being 1.56, 1.83, 1.68, and 1.47 mg. per 100 cc. The pyruvic acid curve in 16 women whose babies weighed more than 10 lb. and whose glucose curve is diabetic in configuration ("recent diabetics") shows a peak value later than the normal, i.e., at two hours rather than at the one-hour level. These values are 1.75, 1.96, 2.11, and 1.86 mg. per 100 cc. The greatest difference in means occurs between the pyruvate levels of the recent diabetics and of the prediabetics at the two-hour level. When analyzed for statistical significance, $t=2.81$ ($P<0.01$); hence, with the oral glucose-tolerance test the two-hour pyruvate values show the widest divergence of means between recent diabetics and prediabetics, and this finding very likely could not have resulted from chance factors.

With the intravenous glucose-tolerance test the nine normal subjects showed an

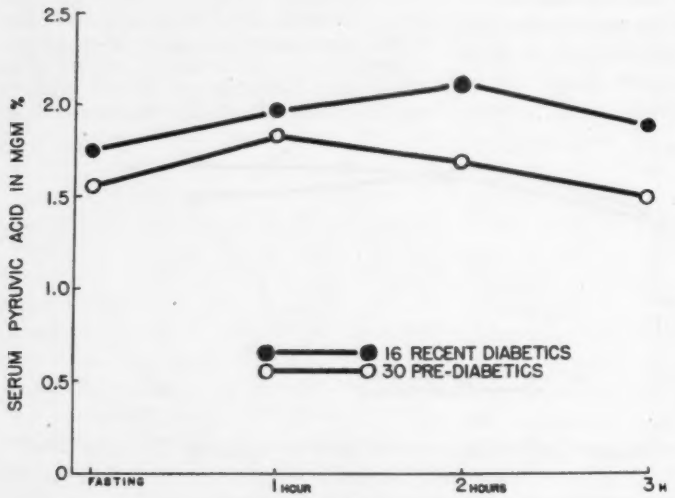


Figure 2

MEAN SERUM PYRUVIC ACID DURING ORAL GLUCOSE TOLERANCE TEST IN PREDIABETIC WOMEN

TABLE 1.—*Serum Pyruvic Acid Response to Orally Administered Glucose in Normals, Persons with Mild Long-Standing Diabetes, Prediabetic Women, and Persons with Recent Diabetes*

	Time, Hr.	Mean, Mg./100 Cc.	S. D., Mg./100 Cc.
Normals (20 subjects)	0	1.63	± 0.43
	1	1.90	± 0.50
	2	1.79	± 0.43
	3	1.69	± 0.46
Mild long-standing diabetes (13 subjects)	0	1.55	± 0.53
	1	1.80	± 0.57
	2	1.90	± 0.55
	3	1.91	± 0.46
Prediabetic women (30 subjects)	0	1.56	± 0.44
	1	1.83	± 0.39
	2	1.68	± 0.43
	3	1.47	± 0.43
Recent diabetes mellitus (16 subjects)	0	1.75	± 0.72
	1	1.96	± 0.44
	2	2.11	± 0.59
	3	1.86	± 0.69

initial rise and then a gradual fall similar to that encountered with the oral test, the specific values being 1.49, 1.69, 1.78, 1.62, 1.52, and 1.34 mg. per 100 cc. However, the eight diabetics, in every instance but one, exhibited a drop in serum pyruvate at both the 30- and 60-minute levels, viz., 1.59, 1.39, 1.39, 1.59, 1.60, and 1.29 mg. per 100 cc. (Table 2 and Fig. 3).

TABLE 2.—*Serum Pyruvic Acid Response to Intravenous Glucose in the Normal and in Mild Long-Standing Diabetes Mellitus*

Time, Min.	Normals (9 Subjects)		Diabetes Mellitus (8 Subjects)	
	Mean, Mg./ 100 Cc.	S. D., Mg./ 100 Cc.	Mean, Mg./ 100 Cc.	S. D., Mg./ 100 Cc.
0	1.49	± 0.28	1.59	± 0.34
30	1.69	± 0.38	1.39	± 0.20
60	1.78	± 0.29	1.39	± 0.33
90	1.62	± 0.42	1.59	± 0.50
120	1.52	± 0.41	1.60	± 0.36
150	1.34	± 0.54	1.29	± 0.30

When the difference Δ between the fasting and 30-minute values is compared algebraically in each individual instance, a significant difference is noted; i.e., the blood pyruvic acid in almost all diabetics dropped, while the most frequent and the greatest rises were recorded in normals (Fig. 4). The mean Δ-30 minutes is +0.19 mg. per 100 cc. for the normal and −0.21 mg. per 100 cc. for the diabetics. Comparable Δ values for fasting and 60-minute levels are +0.28 mg. in the normal and −0.20 mg. in the diabetic. When the raw values at the 30-minute and 60-minute levels are analyzed statistically, $t=2.101$; $P>0.05$ (2.098) for 30-minute values, and $t=2.517$; $P<0.05$ for the 60-minute values. If the Δ values are similarly treated (Table 3), $t=2.5094$; $P<0.05$ for Δ-30 minutes, and $t=2.77$; $P<0.02$ for Δ-60 minutes. Owing to the relatively small sampling and the wide spread of values, the significance of these figures from a mathematical standpoint is equivocal; yet it is believed that these preliminary studies show a definite trend for an early drop in pyruvate in diabetics when the intravenous glucose-tolerance test is used.

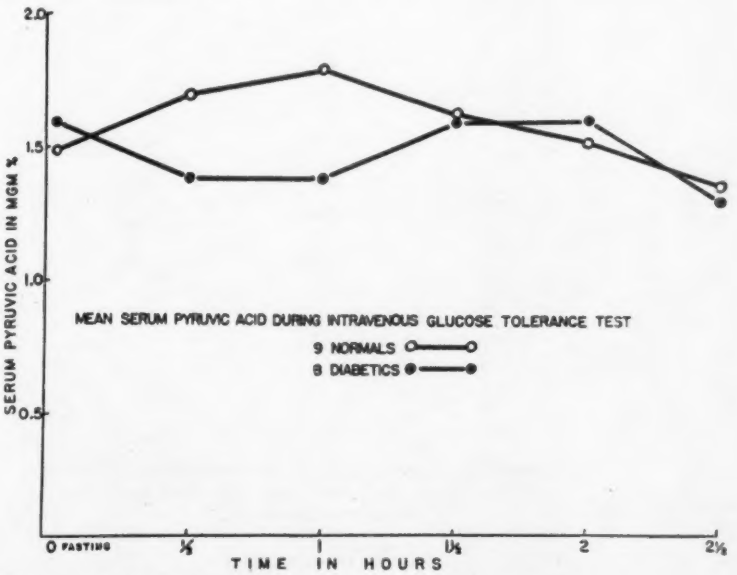


Figure 3

Comment

The above experiments demonstrate two interesting phenomena: First, in contrast to the results in normal subjects, the pyruvate curve in human diabetics is dependent upon the route of administration of glucose. Following oral administration of glucose in the diabetic, the blood pyruvic acid grad-

ually rises and then declines. When the intravenous route is employed the pyruvate first falls, then rises, only to drop again. This altered response, varying with route of administered glucose, was previously noted with reference to serum inorganic phosphorus, wherein normal subjects exhibited a greater and earlier fall in phosphate than did diabetics, but only during the intravenous glucose-tolerance test. No appreciable difference between groups was noted when the oral route was used.[13] No definitive explanation is available at present to account for this observation. One might postulate that the interposition of the liver after glucose is ingested could, in the diabetic, either increase the formation of pyruvate or delay its further breakdown. Conversely, when glucose is given intravenously the portal transport to the liver is by-passed, with a resultant decrease in blood pyruvic acid. This is highly speculative, however, and must await further work with simpler systems and more direct methods. Nevertheless, it would certainly appear that the diabetic metabolizes pyruvic acid differently than the normal when glucose is given intravenously.

The other interesting fact revealed by the data is that the concentration of blood pyruvic acid decreases in the diabetic following intravenous administration of glucose, as had been demonstrated earlier by Amatuzio. An elevation of blood pyruvate is usually attributable either to increased activity of the Embden-Meyerhof glycolytic cycle or to a block in the normal utilization of pyruvic acid in the Krebs cycle. An early

TABLE 3.—*Difference (Δ) in Serum Pyruvic Acid Between Fasting and Subsequent Values During Intravenous Glucose-Tolerance Test*

	Normals (9 Subjects)		Diabetes Mellitus (8 Subjects)	
	Mean, Mg./100 Cc.	S. D., Mg./100 Cc.	Mean, Mg./100 Cc.	S. D., Mg./100 Cc.
Δ ½ hr.*	+0.19	± 0.41	−0.21	± 0.20
Δ 1 hr.†	+0.28	± 0.55	−0.20	± 0.17

* t=2.5094; $0.05 > P > 0.02$.
† t=2.77; $0.02 > P > 0.01$.

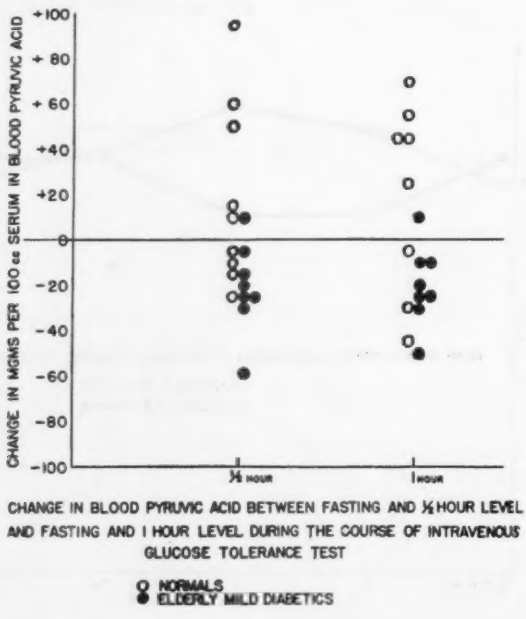


Figure 4

drop of blood pyruvic acid as noted in the diabetics in this series, however, could best be accounted for on the basis of one of three theoretical possibilities:

1. Decreased formation of pyruvate by a slowing of the glycolytic cycle with normal removal through oxidation in the Krebs cycle or through conversion to lactic acid. If one is to assume a primary defect in the hexokinase reaction in the diabetic,[17] then this decrease in blood pyruvate could possibly be due to normal utilization of pyruvic acid and/or a retardation of the glycolytic cycle which depends on the phosphorylation of glucose with hexokinase as a catalyst. The failure to demonstrate this when glucose is administered by mouth demands more explicit explanation.

2. Normal production of pyruvic acid, but with increased removal through the Krebs cycle.

3. The pyruvic acid content of the blood might shift into the cells and hence result in a drop in the blood level.

The latter two hypotheses can not be confirmed by any available evidence in the scientific literature.

Further studies appear worth while in an attempt to answer the above questions bearing upon the fundamental problems of intermediary metabolism and to clarify the diabetic's altered metabolism of substances other than carbohydrate.

Summary

Following the oral administration of glucose, normal and prediabetic subjects show a prompt rise followed by a gradual fall in the blood level of pyruvic acid. In the person with long-standing mild diabetes, the blood pyruvate rises gradually during the entire procedure, while the recent diabetic exhibits a similar slow steady rise, but with a terminal drop.

In normal persons, during the intravenous glucose-tolerance test the blood pyruvic acid roughly parallels the blood sugar, whereas in the diabetic the pyruvate first decreases, then increases, and then falls again.

It is suggested that the early drop in pyruvate following intravenous glucose in the diabetic may be due to retarded glycolysis.

Future work, particularly with experimental animals or isolated tissues, should help explain these observations.

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Carbohydrate Metabolism in Brain Disease

VI. Lactate Metabolism After Infusion of Sodium *d*-Lactate in Manic-Depressive and Schizophrenic Psychoses

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Two earlier studies from this laboratory showed that abnormally large amounts of lactic acid accumulate in the blood after administration of glucose [1] or fructose [2] in many patients with schizophrenic or manic-depressive psychoses. Another study [3] showed that administration of corticotropin (ACTH) or hydrocortisone to psychotic patients who did not have this abnormality regularly produced it. Other observers had previously demonstrated a disturbance of lactate metabolism during exercise in these psychoses.* In view of these findings, it was decided to study the effects of intravenously infused sodium *d*-lactate in normal and psychotic subjects.

Materials and Methods

Ten grams of *d*-lactate, in the form of the sodium salt, was dissolved in 500 ml. of isotonic salt solution and given intravenously in 30 minutes. Blood samples were taken before and at the end of the infusion and again 15 and 30 minutes later. The methods used were as previously described.†

The subjects ranged in age from 17 to 48 years. Twelve were not psychotic; seven had schizophrenic or manic-depressive psychoses of recent onset, and five had chronic psychoses. Four of the patients in the second group were restudied after treatment, shortly before they were discharged improved.

Observations

The control values ranged between 4.3 and 12.75 mg. per 100 ml. in the normal subjects; the average was 7.6 mg. Seven patients with psychoses of recent onset had blood lactate concentrations of 6.3 to 8.75 mg. per 100 ml.; the average was 7.2 mg. per 100 ml. of blood. The values in the five chronically psychotic patients were between 3.5 and 12.0 mg. per 100 ml.; the average was 6.9 mg. per 100 ml. of blood.

The blood lactic acid levels at the end of the period of infusion varied markedly among the subjects but did not differ among the various groups of patients. However, 15 minutes after the end of the infusion the lactate concentration was more than 3 mg. per 100 ml. above the control value in only 3 of 10 nonpsychotic subjects so studied, whereas 6 of 6 patients with psychosis of recent onset and 3 of 4 with chronic psychoses showed elevations of this degree. None of the patients who were discharged improved exhibited this finding (Figs. 1 and 2). Combining the two untreated psychotic groups provided enough patients for statistical comparison with the nonpsychotic subjects. The χ-square test yielded a value of 5.21, with a P value of <0.05.

Measurements made 30 minutes after the end of infusion showed concentrations greater than 1.5 mg. per 100 ml. above the control values in only 1 of 12 non-

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* References 4-7.

† References 1-3.

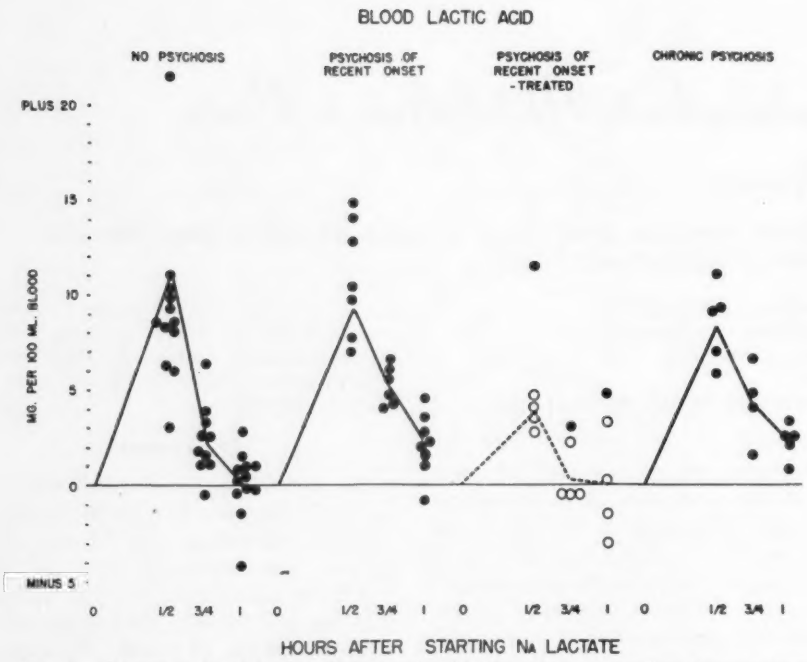

Fig. 1.—Changes in blood lactic acid level after infusion of 10 gm. sodium *d*-lactate intravenously. The open circles indicate patients improved after treatment. The averages are indicated by lines, a broken line being used for the patients improved after treatment.

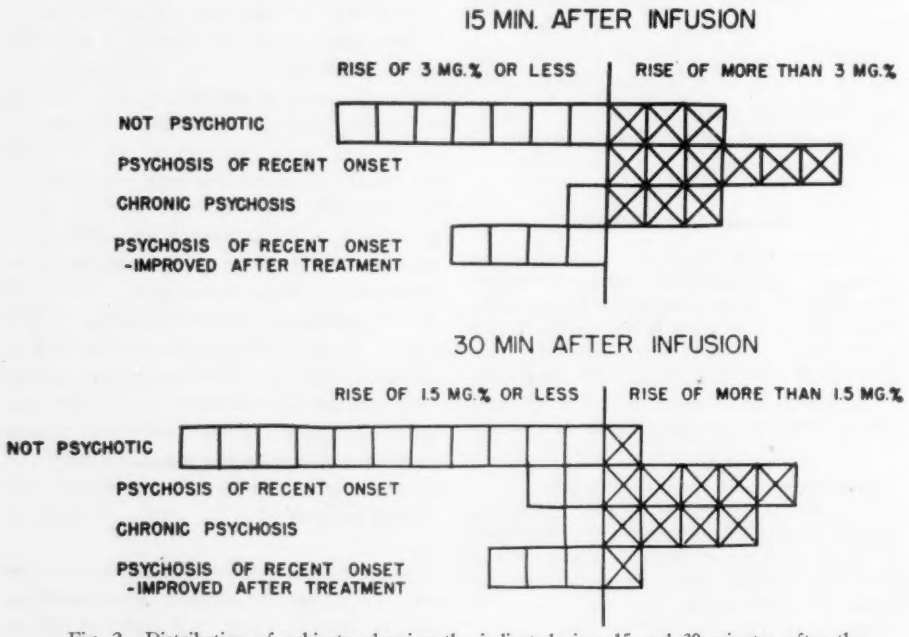
15 MIN. AFTER INFUSION
RISE OF 3 MG.% OR LESS
RISE OF MORE THAN 3 MG.%
NOT PSYCHOTIC
PSYCHOSIS OF RECENT ONSET
CHRONIC PSYCHOSIS
PSYCHOSIS OF RECENT ONSET -IMPROVED AFTER TREATMENT
30 MIN AFTER INFUSION
RISE OF 1.5 MG.% OR LESS
RISE OF MORE THAN 1.5 MG.%
NOT PSYCHOTIC
PSYCHOSIS OF RECENT ONSET
CHRONIC PSYCHOSIS
PSYCHOSIS OF RECENT ONSET -IMPROVED AFTER TREATMENT

Fig. 2.—Distribution of subjects, showing the indicated rises 15 and 30 minutes after the end of infusion of 10 gm. of sodium *d*-lactate.

psychotic subjects, whereas 5 of 7 patients with psychoses of recent onset and 4 of 5 with chronic phychoses showed this finding. One of four of the treated patients discharged improved had a blood concentration elevated to this degree (Figs. 1 and 2). Combining the two untreated psychotic groups provided enough patients for statistical comparison with the nonpsychotic subjects. The χ-square test yielded a value of 8.40, with a P value of < 0.01.

Another type of statistical analysis also was made. Combining both groups of psychotic patients and calculating standard errors from the actual values 15 and 30 minutes after the end of infusion yielded the following statistics:

Mean Rise in Lactic Acid Level	Standard Error, Mg./100 Ml.		
	Not Psychotic	Psychotic	P
15 min. after the end of infusion	2.30 ± 0.58	4.78 ± 0.48	<0.01
30 min. after the end of infusion	0.04 ± 0.50	2.27 ± 0.40	<0.01

Comment

There is a slight lag in the disappearance of lactic acid in psychotic patients after the infusion of 10 gm. of that substance as the sodium salt. However, this degree of impairment of lactate metabolism is far smaller than that observed after injection of lactate in patients with liver disease ‡ or with anoxic disorders such as anemia,§ cardiac decompensation,‖ or pulmonary disease.[10] In these conditions the injection of smaller amounts of lactate than used here caused more striking abnormalities than occur in mental disease.

Löwenbach and Greenhill [15] found abnormally large rises in blood lactate concentration after feeding approximately 40 gm. of it to patients with depressions. In addition, earlier workers observed excessive rises in blood lactic acid level after exercise in schizophrenia ¶ and in manic-depressive psychosis.[4] A similar, though apparently less marked, change also occurs in neuroses after exercise.# The occurrence of the same phenomenon in the various anoxic states listed above is to be expected,[20] but it also has been found in various somatic disorders not associated with anoxia, such as hyperthyroidism * and liver disease † and in the absence of disease during convalescence from a variety of illnesses.‡ All available evidence indicates that an enzymatic disturbance that impedes the removal of lactate from the blood stream occurs in many different bodily diseases; the disturbance is especially severe in liver disease and in anoxic disorders but may occur without either. It is evident that it also occurs in the psychoses studied here.

The reason for the delayed removal of lactate from the blood in psychotic patients is not apparent. One possible explanation is that the transformation of lactate to glycogen is impaired; there is no information bearing on this point. Another possibility is that the lactate that enters the metabolic pool is utilized with abnormal slowness. The degree to which lactate enters the metabolic pool in resting man has never been defined; accordingly, the second possibility likewise cannot yet be evaluated. At any rate, the present study shows that patients with schizophrenic and manic-depressive psychoses have a disturbance in lactate metabolism that is qualitatively similar to one found in many somatic disorders.

Conclusions

Disappearance of injected sodium *d*-lactate from the blood stream is somewhat slower than normal in patients with schizophrenic or manic-depressive psychoses. This impairment of lactate metabolism, though not severe, resembles that found in a variety of bodily diseases.

‡ References 8 and 9.
§ References 10 and 11.
‖ References 9-14.
¶ References 5-7.
# References 16-19.
* References 21-24.
† References 21 and 25.
‡ References 17 and 25.

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Splenoportography for the Diagnosis of Portal Hypertension

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The portal hypertension syndrome embraces two separate types of cases: the intrahepatic group, where the blockage is within the liver, and the extrahepatic group, where the obstruction is situated in the portal vein or one of its radicles outside the liver. Opacification and visualization of the portal vein is, therefore, a valuable diagnostic guide to what is essentially a surgical problem. It not only enables a differential diagnosis by demonstrating the site of obstruction but also confirms the diagnosis of portal hypertension, provides information concerning the status of the involved vessels, and indicates the presence of anomalies. Splenoportography, a comparatively recent development, represents a clinically proved, useful, and safe technique for visualizing the portal vein without surgical intervention.

Credit for having first applied the method of portal vein opacification by splenic puncture belongs to Abeatici and Campi,[1] who published the results of their test, initially carried out in dogs and subsequently in human subjects. Opacification of the portal vein had previously been performed through catheterization of one of its related vessels during surgical procedures. Another means of visualization, employed in the presence of Cruveilhier-Baumgarten's syndrome, has involved catheterization of the umbilical vein.

After publication of the work of Abeatici and Campi [1] many other studies were reported in medical literature throughout the world, including those of Leger,[2] Sotgiu,[3] Dreyer,[4] and Rousselot.[5] The purpose of this paper is to report our experience with percutaneous splenoportography at the Nutritional Diseases Hospital. Our objective is demonstration of the usefulness of the procedure, with particular emphasis on its safety.

Materials and Methods

Eleven patients with portal hypertension, showing esophageal varices and splenomegaly, were studied. Nine had cirrhosis of the liver, and the other two evidenced extrahepatic obstruction. Their maximal age was 60 years, and the minimal age, 9 years. In addition to these cases, the method was employed on seven other patients who manifested various ailments. We have applied, with small modifications, the technique originally delineated by Abeatici and Campi.

The spleen is localized by percussion. Through a plain anterior-posterior film of the abdomen, we measure the thickness of the spleen; adequate correction is obtained by multiplying by 0.8 or by using a Colcher-Sussman pelvimeter ruler. These data give us the depth of the injection. The site is usually between the 9th and 10th left intercostal spaces on the middle or anterior axillary line.

After the abdominal wall is anesthetized, the needle is introduced to the desired depth when the patient is in midrespiration. Blood appears readily when the needle enters the splenic pulp. Just at this time, the needle is connected to a membrane electromanometer and a tensiometric tracing

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is taken by means of an electrical device. This procedure serves to register the portal vein pressure. Immediately afterward, 30 cc. of 70% iodopyracet (Diodrast *) is injected within a period of four seconds. For this purpose a No. 18 needle is used. Immediately thereafter, and with the needle in place, a radiograph is taken. The patient must hold his breath while the injection and the exposure are made. The entire process from the puncture to the exposure of the radiography requires no longer than half a minute.

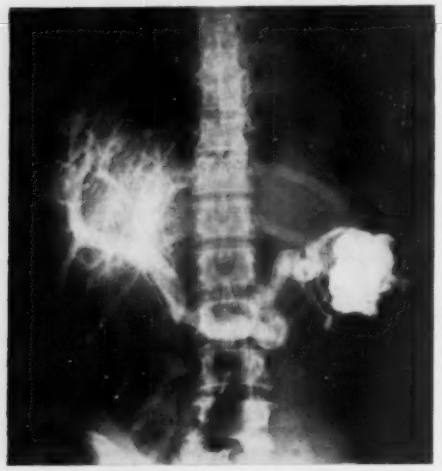

Fig. 1.—Normal splenoportography. This patient had splenomegaly due to chronic malaria, with no evidence of portal hypertension. Note the absence of hepatofugal filling.

We have never used a rapid film changer. Although we realize the value of a series of radiographs made in rapid succession, we find that in a majority of the cases an exposure made at the end of the injection is sufficient to enable us to make conclusions of practical clinical value (Fig. 1).

The use of the membrane electromanometer does not lengthen the time of the procedure. The reading of the figures that are registered, which is in itself very useful, helps to ascertain the correct placement of the needle.

* Winthrop-Stearns, Inc., New York.

Results

It has been our experience that the contraindications for splenoportography are pronounced tendency to hemorrhage, infectious splenomegaly, and the presence of ascites, which must be aspirated prior to attempting visualization.

We have not observed any serious accidents in our group of patients. In one person the needle ran through the splenic parenchyma (Fig. 2). Subsequently, this patient died of a hemorrhage due to rupture of the esophageal varices, and at the necropsy a hematoma of the splenic hilum was found. In cases in which an examination of the spleen was made during surgery or at autopsy of patients who died of other causes only small subcapsular hemorrhages were observed.

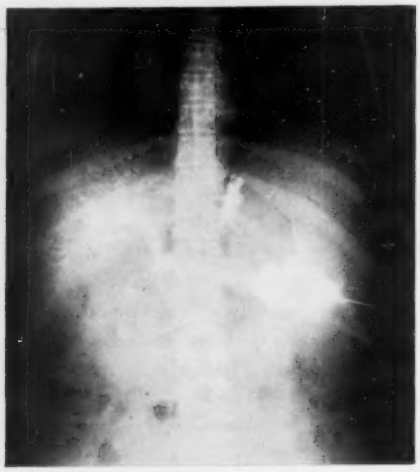

Fig. 2.—Portal hypertension due to chronic liver cirrhosis. The needle ran through the splenic parenchyma. Notice the pooling of opaque material in the hilum. There is good hepatofugal filling of the coronary vein and demonstration of gastric varicosities. There is good filling of the intrahepatic portal chanels. Notice the small size of the liver.

On several occasions the radiopaque substance was partially or totally spilled into the peritoneal cavity, so that visualization of the portal system was hindered. We have never observed any side-effects of importance. The drug is absorbed by the peritoneum and eliminated by the kidneys

in a period of two hours. Only a few patients complained of pain in the left shoulder, which disappeared in a short time and required no treatment.

All these incidents were occasioned by faulty technique in performing the splenic puncture. Although allergic reactions were not encountered, a routine intravenous sensitivity test with 1 cc. of the contrast medium is recommended.

The studies were carried out only on

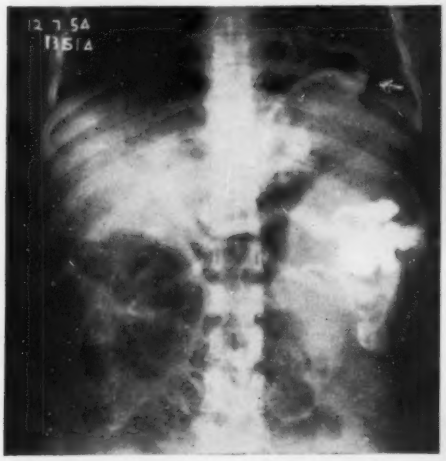

Fig. 3.—Portal hypertension due to chronic liver cirrhosis. Notice the small amount of opaque material spilled in the peritoneal cavity. There is good hepatofugal filling, demonstration of gastric varices, and filling of intercostal veins (arrow).

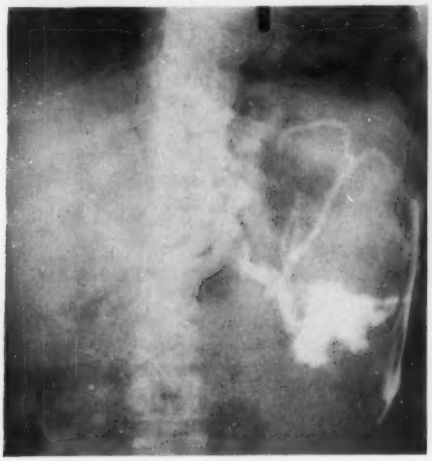

Fig. 4.—Portal hypertension due to chronic liver cirrhosis. The spleen is greatly enlarged. Opaque material has spilled in the peritoneal cavity. There is hepatofugal filling of short gastric veins, through the gastrosplenic omentum. There is filling of the coronary vein and the gastric and esophageal varices.

Fig. 5.—Portal hypertension due to thrombosis of portal vien. There is hepatofugal filling of short gastric veins and gastric and esophageal varices. The splenic vein is well filled, but there is no opacification of the portal vein.

Fig. 6.—Same case as shown in Figure 5. Through a catheter inserted in the superior mesenteric vein, there is good filling of the splenic vein and gastric varices and partial filling of the coronary vein. Notice the great collateral circulation in the territory of the superior mesenteric. No filling of the portal vein is seen. At necropsy a large thrombus of the portal vein associated with chronic cirrhosis was found.

hospitalized patients and under close supervision to enable rapid detection of any complications. As a precaution against hemorrhage, the method was employed only in patients who were scheduled for surgical intervention. The injection was given only a short time before the patient was taken to the operating room. At present, however, we do not take this precaution, since it has been demonstrated that the splenic puncture does not produce hemorrhage.

In cases of failure, the study was repeated a week later to allow for healing of the spleen.

Indications

The principal advantage of splenoportography may be summarized as follows:

(*a*) To confirm a diagnosis of portal hypertension. This is accomplished, first, by reading the figures on the manometer—before the contrast substance is injected—and, second, by demonstrating the hepatofugal circulation (Figs. 3 and 4).

(*b*) To determine the site of the obstruction. It is well known that it is extremely difficult, if not impossible in some cases, to make a differential diagnosis between portal hypertension caused by intrahepatic obstruction (cirrhosis) and that caused by an extrahepatic block. Percutaneous splenoportography helps to make such a differential diagnosis, as demonstrated by our work and that of other clinicians who have used this method (Figs. 5 and 6).

(*c*) To obtain information concerning the status of the vessels. We have found a fibrotic portal vein which, in addition to being the cause of the hypertension, rendered the vessel entirely unfit for a portacaval anastomosis. In a case like this, splenoportography can prevent an unnecessary operation which might endanger the life of the patient (Fig. 7).

(*d*) To demonstrate anomalies. We have been able to show anomalies of the splenic vein which make it unfit for splenorenal anastomosis (Fig. 8).

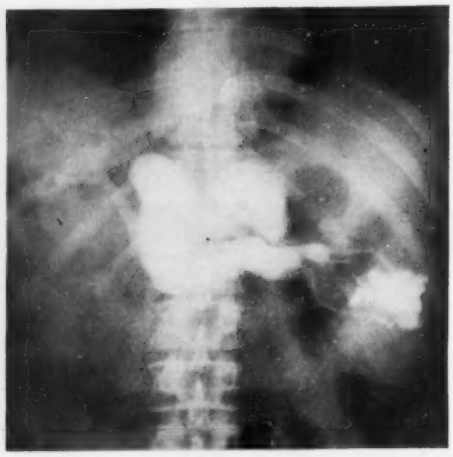

Fig. 7.—Portal hypertension due to fibrosis of the portal vein. There is splenomegaly and hepatofugal filling of a large tortuous coronary vein. The portal vein is extremely narrow. In this case splenoportography was done after an unsuccessful attempt to perform a portacaval shunt.

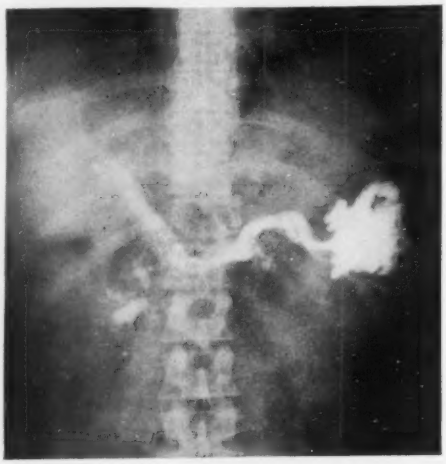

Fig. 8.—Chronic liver cirrhosis with portal hypertension and chronic pancreatitis. Notice that the splenic vein is formed by two veins that go almost to the middle line. There is hepatofugal filling of the coronary vein.

Summary and Conclusions

Percutaneous splenoportography is a safe and diagnostically valuable procedure, as evidenced by the series of cases presented in this paper. The chief usefulness of the method rests with its ability to offer the

following information: (1 confirmation of the existence of portal hypertension, (2) localization of the site of obstruction, and (3) demonstration of anomalies of the portal system.

We believe that with increasing application of this procedure more complete understanding of the portal circulation will be possible.

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A Malabsorption Syndrome in Military Personnel in Puerto Rico

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Introduction

The diagnosis of tropical sprue in Puerto Rico has been defined in the studies of Suarez [1] and Rodriguez-Molina.* Patients with this diagnosis have had macrocytic anemia and megaloblastic bone marrow changes associated with diarrhea, dyspepsia, weakness, and weight loss. They have been treated with liver extract, folic acid, and cyanocobalamin (vitamin B_{12}), with excellent hematologic remission. An explanation for the disease has been attributed to nutritional deficiency, inasmuch as the majority of the patients have been indigent and have had poor dietary habits. The hematologic abnormalities have received major attention, and justly so, in an effort to rehabilitate the patients. However, such interest has emphasized the bone marrow dyspoiesis as the outstanding pathological physiology. This criterion is in striking contrast to sprue as observed in other tropical areas of the world. Anemia was not a prominent observation in the large series of sprue patients that were published by workers in Southeast Asia (India) after World War II. Stefanini [4] observed a macrocytic anemia in 14% of 1069 cases in Italian prisoners of war. Elder [5] observed macrocytic anemia in 22% of 400 cases in British troops; Keele and Bound [6] found hemoglobin values below 12 gm. in 24% of 600 cases. These large series emphasize that macrocytic anemia need not be a prominent feature of the disease in well-nourished persons. It is assumed that the patients without macrocytic anemia had no megaloblastic changes of the bone marrow. Likewise, iron-deficiency anemia was rare.

The persistent criterion of a hematologic defect in the diagnosis of tropical sprue in Puerto Rico has led to an assumption that a different disease may exist in the Caribbean area that is a more specific nutritional deficiency in contrast to the disease as seen elsewhere in well-nourished persons. Possibly the condition of the anemic sprue patient studied in Puerto Rico represents a more advanced nutritional deficiency, inasmuch as in the past economic stress has provided a marginal subsistence. Hence, the onset of malabsorption has resulted in a more fulminating manifestation of megaloblastic anemia.

During the past year efforts have been made to evaluate complaints of diarrhea among the military personnel stationed in Puerto Rico to determine whether a malabsorption syndrome similar to the type observed by British investigators exists in this Caribbean area. Patients were studied who had diarrhea for several weeks to months. Special effort was made to find patients who had marked lassitude and anorexia with diarrhea. As the study was initiated and patients were treated, some military personnel with similar complaints instituted self-treatment with folic acid; consequently many patients were not studied who had previous complaints of chronic diarrhea. Twenty-one cases were observed in which evidence of malabsorption associated with diarrhea and without anemia existed. These patients have been of special interest because they represent a type of

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* References 2 and 3.

malabsorption syndrome that has not been described in this area. Finally, the nutritional aspects of the disease can be ignored in the majority of these patients in view of the variety of food items available.

Clinical Observations

Patients were observed on the medical wards or outpatient clinics of Rodriguez Army Hospital.† Nineteen male and two female patients were studied. Eleven patients were commissioned officers; five were noncommissioned officers. Ages varied from 22 to 47 years; 11 patients were in the third decade. Six patients were natives of Puerto Rico; the remainder, on overseas military duty from the United States. No past history of childhood gastrointestinal disorders was elicited in any of the group.

An outline of the symptoms observed in these patients is presented in Table 1. The duration of illness is also listed in Table 1, according to the patients' statement, although the insidious character of the diarrhea made it difficult to define onset accurately. In two instances the diarrhea and lassitude occurred one month before the patient was seen and within a period of a few months after arrival in Puerto Rico. Intermittent diarrhea is a common complaint among the civilian population, and the onset of symptoms among Puerto Rican military personnel also was difficult to define. All of the patients had diarrhea which varied in frequency from 2 to 10 stools in a 24-hour period. The diarrhea did not exist necessarily as a daily abnormality. At the onset, frequency of bowel movements varied, with periods of diarrhea alternating with normal bowel habits for several days. However,

TABLE 1.—*Summary of Signs and Symptoms*

Case	Age, Yr.	Weight Loss, Lb.	Duration of Symptoms, Mo.	Weakness and Lassitude	Diarrhea*	Dyspepsia or Anorexia	Abdominal Cramps	Glossitis
1	41	30	3	+	+	+	+	0
2	29	18	2	+	+	+	+	0
3	25	30	2	+	+	+	+	0
4	32	20	2	+	+	+	+	0
5	28	35	12	+	+	+	+	+
6	28	9	5	+	+, I	+	+	0
7	27	14	7	+	+	+	+	0
8	26	10	2	+	+	+	+	0
9	27	20	4	+	+	+	+	0
10	31	12	3	+	+, I	+	+	0
11	22	19	2	+	+	+	+	+
12	26	18	12	+	+	+	+	0
13	46	17	4	+	+	+	0	0
14	31	23	4	+	+, I	+	0	0
15	30	13	4	+	+	+	+	0
16	47	10	1	+	+	+	0	0
17	27	40	4	+	+	+	+	0
18	33	15	12	+	+	+	0	0†
19	33	19	5	+	+	+	+	+
20	26	5	1	+	+, I	+	0	0
21	23	5	2	+	+, I	+	0	0

* I indicates that diarrhea was intermittent.
† Buccal mucosal burning, but none of the tongue.

† The continued cooperation of Col. Leon J. Numainville (MC) and his staff made these observations possible.

often in the absence of diarrhea the stools were soft and mushy and the patient noted explosive flatus. A few patients were certain that the stool was firm, and according to their description they were free of symptoms for periods of several days. During episodes of diarrhea the stools were watery, sometimes frothy and malodorous. They floated on water and were light yellow-tan. Pale putty-colored stools were not described, and greasy stools with fat globules were not observed by patients, even after they were questioned. Patients noted abdominal cramps before they had bowel movements; sometimes the cramping was very painful. Two patients were considered to have peptic ulcers because their initial complaint was epigastric pain. Nausea following meals was a common complaint, and numerous patients described episodes of vomiting. Most of the patients could associate the abdominal distress with meteorism and excessive flatus.

Some degree of anorexia was noted in all but one patient. There was a good selection of diet, since patients could eat at home away from a military installation, and often the patient had eliminated fried foods and gravies from the diet by trial-and-error method. None of the patients decreased food intake markedly to control diarrhea. With the diarrhea and anorexia the patients complained of lassitude and weakness. The feeling of weakness and inability to perform at work was the greatest concern of the patients, since they had anticipated diarrhea to be a complication of a tropical assignment. The patients often attributed the lassitude and poor work performance to the warm tropical climate. Again, it was difficult to define onset of these symptoms; certainly the onset was not abrupt.

Glossitis was observed in three patients; two had changes that consisted of reddened borders and papillary atrophy of the tip of the tongue only. These patients had only mild sensation of burning when eating. One patient (Case 5) had marked reddening of the tongue associated with constant burning sensation of the tongue and esophagus. It was necessary to give him bland liquid feedings for a period of several weeks while he was under investigation. One patient described burning of the buccal mucosa, but there were no visible changes.

Although all patients had lost weight, these values are estimations, inasmuch as comparisons were made with the weight obtained on the hospital scale. Despite the moderate weight loss, no one had evidence of malnutrition or emaciation. Stool examinations for ova, parasites, and dysenteric organisms were performed on all patients. One patient had hookworm infestation, and another patient had Ascaris lumbricoides. However, successful specific therapy did not alter the patients' diarrhea. Hematologic values were normal for the entire group. Bone marrow studies were not done, and reticulocyte responses during therapy were not followed. Liver function was not abnormal as measured by serum bilirubin, thymol turbidity, or sulfobromophthalein (Bromsulphalein) excretion.

Diagnostic Studies

Radiological Examination.—All patients in this study had at least one radiologic examination of the small bowel as part of the diagnostic investigation before treatment. The small bowel was observed after a test meal consisting of a mixture of 80 gm. of barium sulfate suspended in 250 ml. of water. No stabilizing agents were incorporated in the barium mixture. On the initial examination a careful fluoroscopic study of the stomach and duodenum was done and films were taken at half-hour intervals for a two-hour period. Some patients had more than one examination of the small bowel if they had been fluoroscoped previously with a presumptive diagnosis of a peptic ulcer. No peptic ulcers, however, were observed in this group. After varying lengths of time following folic acid therapy, the small bowel pattern was reevaluated in the same fashion. The criteria of Adlersberg[7] were used to denote changes in the small bowel films.‡

Special Laboratory Studies.—Routine hospital laboratory studies were done in all cases, and oral absorption—tolerance tests and fat-balance studies

‡ Capt. Keith Irish (M C) performed and aided in the interpretation of these studies.

were performed on some of the patients in this series. Similar observations were made on volunteer subjects free of gastrointestinal complaints to allow comparison of results with the patients under study. Four oral absorption-tolerance tests were utilized: glucose, D-xylose, vitamin A, and butter fat. The oral glucose-tolerance test was performed by administering 100 gm. of glucose in 500 ml. of water. Venous blood samples were collected before administration and at one-half, one, two, and three-hour periods. Blood sugar values were determined by the Folin-Wu method.

Some patients were given an oral tolerance test utilizing 25 gm. of D-xylose in 500 ml. of water. Venous blood samples were collected hourly over a five-hour period. A urine sample for the five-hour test period also was collected. Later in the study only the five-hour urinary excretion of D-xylose was used. The urinary excretion appeared to reflect changes in the malabsorption syndrome sufficiently well for it to be used as a preliminary screening procedure. Blood and urine values were determined by the method of Brien[9] and coworkers.

Fat-soluble vitamin A has been considered a good index of fat absorption. The fasting patient was given 300,000 units of vitamin A in percomorph liver oil (60,000 units/ml). Blood samples were collected prior to administration and at three and five hours. The patient was then allowed a full meal, to determine whether vitamin A absorption could be further enhanced by intestinal motility associated with digestion.[10] Later in the study, the three-hour sample was no longer obtained. Serum levels of vitamin A were measured with the Carr-Price reaction by the method of Consolazio.[11] The results were expressed in micrograms per 100 ml. of serum, with a standard vitamin A alcohol solution as a reference. The procedure was modified only by using ethylene dichloride as an antimony trichloride solvent, inasmuch as the chloroform solvent is not satisfactory in a humid tropical area.[12] Serum carotenoids were determined to allow correction for the serum vitamin A measurements.[13]

A butter-fat-tolerance test similar to the procedure used to evaluate blood chylomicron changes was utilized, as outlined by Frazer and Stewart.[18] A breakfast meal of 30 gm. of butter, two pieces of toast or six soda crackers, 100 ml. of fruit juice, and one cup of tea or coffee with sugar was fed to the patients. Fasting and five-hour samples of blood were collected. During the test period patients were kept quiet and not allowed to smoke. The clotted samples of blood were allowed to retract at room temperature for several hours and were then centrifuged at 2000 g for 15 minutes. The fasting serum was used as a blank sample in the Coleman spectrophotometer at 650μ wave length. The optical density in the hourly samples was read and plotted against time. Early in these studies efforts were made to do chylomicron counts on the same serum samples, following the technique of Frazer and Stewart.[18] However, the reproducibility of the counting by several observers was not satisfactory. Also, since the samples were collected at some distance from the laboratory, adequate time was not available to process the material.

To determine the total amount of dietary fat absorbed, a fat-balance analysis was done in 13 patients. A calculated diet containing 70 gm. of fat and 90 gm. of protein was used. Approximately 50 gm. of the dietary fat was derived from milk and butter. The total diet contained 2000 Calories. Patients were allowed variations in fruits and vegetables. The diet periods were maintained for 10 days but were extended in volunteer patients. Stools were collected for 24-hour periods and were assayed daily. Fecal fat was determined by measurement of the total fatty acid content by the method of Van de Kamer.[14] No further elaboration of determination of fat excretion in the form of volatile fatty acids or soaps was done. The daily fat excretion was plotted as an average of a running three-day mean. This procedure tends to level out irregularities arising from sampling errors.[15]

Duplicate samples of the diet were collected, ground, and blended. The same procedure utilized in determining fecal fat was used to calculate the dietary fat consumed. Six volunteer soldiers who had no gastrointestinal symptoms each consumed the test diet for a 12-day period to allow comparative values in normal subjects.

Fasting serum iron levels were determined in 13 patients, and an index of iron absorption was estimated by feeding the patient 300 mg. of iron in the form of an elixir of ferrous sulfate. Hourly determinations of serum iron levels for a five-hour period were performed by the ferrocyanide method of Burch.[16]

Results

Radiological Studies.—Twenty-one small bowel studies were done before treatment, and fifteen were completed after varying periods of folic acid therapy. No patient had prolonged transit time for the barium suspension to pass through the small bowel. No assessment was made of excessive rapid transit time. All patients had good visualization of the jejunal pattern outlined in the one-hour film, and this film was used most frequently for comparative evaluation. A summary of the small bowel observations is

TABLE 2.—*Abnormalites of Small Bowel X-Ray Studies**

Case	X-Ray Appearance Before Therapy				Duration of Therapy, Mo.	X-Ray Appearance During Therapy			
	Dilatation	Thickened Folds	Segmentation	Scattering		Dilatation	Thickened Folds	Segmentation	Scattering
1	0	0	+	0	7	0	0	0	0
2	0	0	±	0	7	No follow-up studies done			
3	0	+	+	0	7	0	0	+	0
4	0	+	+	0	4	0	0	0	0
5	+	+	+	0	2½	0	0	0	0
6	0	0	+	0	5	0	0	0	0
7	0	+	+	0	5	0	±	±	0
8	0	0	0	0	5	0	0	0	0
9	0	+	+	+	5	0	0	0	0
10	0	0	+	+	1½	0	0	0	0
11	0	0	0	0	5	No follow-up studies done, as first examination was normal			
12	0	+	0	0	4	No follow-up studies done			
13	0	+	+	0	5	0	0	0	0
14	0	0	0	0	None	No follow-up studies done, as first examination was normal			
15	0	+	+	0	5	0	0	±	0
16	+	+	+	+	2	0	0	0	0
17	0	+	+	0	5	0	0	0	0
18	0	+	+	0	10	0	+	+	0
19	0	+	+	0	5	0	±	0	0
20	0	+	+	0	2	No follow-up studies done			
21	0	0	0	0	2	No follow-up studies done			

* See text for explanations.

presented in Table 2. All abnormal findings are listed (+). In some studies variations were minimal or questionably present; however, they are noted (+). No effort was made to grade the severity of the alterations noted on films taken at half-hour periods. The four criteria selected from Adlersberg [7] for study were the following: (1) dilatation of the small bowel diameter beyond 3 cm.; (2) hypertrophy and thickening of the small bowel mucosal folds; (3) segmentation of the barium meal, with loss of the fine feathery pattern, and (4) scattering of residual barium particles, after passage of the meal. Excessive secretion was not evaluated.

In these early cases dilatation of the small bowel lumen was not a common observation; a diameter of more than 3 cm. was observed in only two patients (Fig. 1). Twelve patients showed coarsening of the barium pattern in the jejunum, which has been attributed to edema of the mucosa and has often been called thickening of the folds (Fig. 2). The abnormality is difficult to measure and has much variation. It may represent the earliest manifestation of the disordered small bowel pattern.

Segmentation of the barium meal in small patterns was the most frequent abnormality observed. The small segments of "puddled" barium were observed in the jejunum and were best seen in the one-hour film. It was difficult to be certain of segmentation in the later films when the barium was in the ileum, for similar aggregates may be present in films of normal patients. In fact, all diagnostic abnormalities should be present in the upper portion of the small bowel (Figs. 3 and 4). In association with the segmentation of barium, large stippled aggregates of barium remained in areas of the bowel that had been otherwise cleared of barium. The term "scattering,"

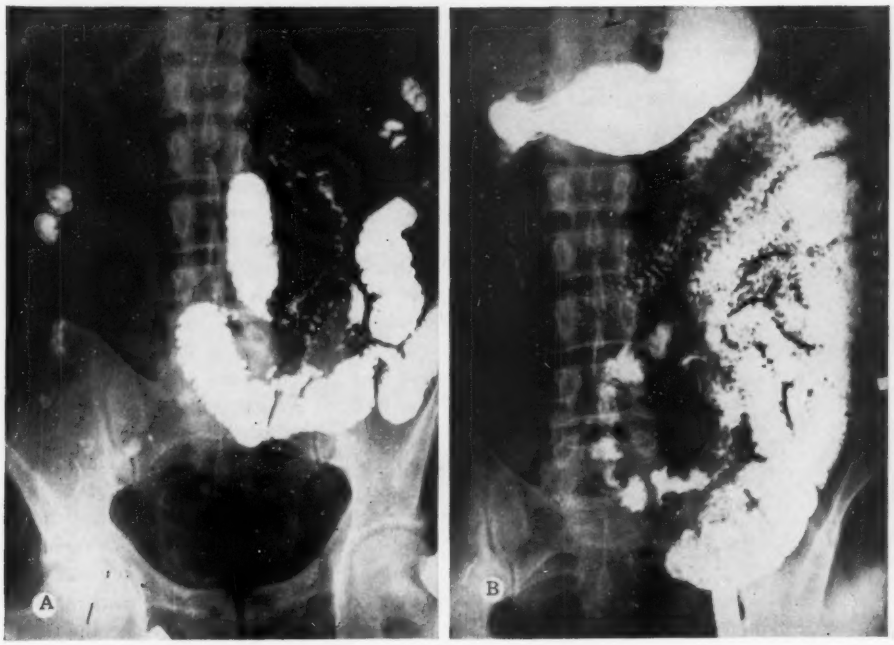

Fig. 1 (Case 16).—*A*, large dilated small bowel segmentation measuring 4 cm. in diameter. *B*, after two months of oral folic acid therapy the patient has normal mucosal pattern and absence of dilatation and segmentation.

as defined by Adlersberg, was used to describe these changes.

Four patients had no abnormalities listed in their initial study. Certainly any abnormal x-ray changes of the bowel pattern were minimal, although they had impaired absorption of vitamin A, butter fat, glucose, and D-xylose. However, it would have been advantageous to have repeated x-ray examination before therapy was started. Limited local x-ray facilities did not warrant a delay in care of the patients to obtain the extra observations of the small bowel. Comparison of the radiologic abnormalities in Table 2 with the fecal fat values in Table 3 indicates poor correlation of the altered bowel pattern with steatorrhea or absorption as defined by oral tolerance tests. These observations do not substantiate the claims of Drew,[17] regarding the efficacy of radiologic study for evaluation of the disease.

After therapy with folic acid, 10 patients had complete reversal of the abnormal signs on the small bowel films. The time period between examinations is noted in Table 2. In view of the reversal of the small bowel pattern in six- and eight-week periods, the x-ray studies should have been done at more frequent intervals for more accurate determination of bowel changes. The present examinations were done as military personnel could be made available from duty and in some instances were not repeated. As the patients improved, it was more difficult to obtain further laboratory and x-ray examinations. Four patients had improvement in the degree of abnormality present but still showed some defects in the barium pattern.

Oral Glucose-Tolerance Test.—Fifteen patients had this procedure prior to therapy. Later in the study this observation was discontinued. It was soon apparent that the blood sugar increment at the one-half and one-hour period were the only necessary

Fig. 2 (Case 12).—Thickening of the folds in the jejunum and ileum. Some small areas of segmentation are present.

levels for evaluation. Only a minimal increase of 25 mg. per 100 cc. rise was used for diagnostic evidence of impaired glucose absorption. As noted in Table 4, the mean rise at one-half hour was 12 mg. per 100 cc., with a range of 0 to 27 mg. per 100 cc. At the one-hour period the increase in blood sugar for the group averaged 15 mg. per 100 cc., with a range of 0 to 38 mg. per 100 cc. None of the patients had an absorption curve that appeared normal. All patients showed impaired absorption of glucose and a persistent "flat curve" of oral absorption.

While these studies were in progress, the large series of control observations in military personnel in Texas by Moyer and Womack[18] was reviewed. These patients were of a similar age group and represented a good comparison for the present investigation. If the increment rise of blood sugar levels from the individual tests for the half-hour period is abstracted from the raw data tabulated, it is apparent that the "flat curve" of glucose absorption has limited significance. A fifth of the 103 subjects of Moyer and Womack had less than a 25 mg. per 100 cc. rise at one-half hour, and 45%, at one hour. Numerous investigators have used a 40 mg. per 100 cc. blood sugar increment as a diagnostic level for malabsorption. If such an increase is evaluated, then 40% of their control subjects had less than 40 mg. per 100 cc. rise at one-half hour and 65%, at one hour.

To evaluate whether the normal population has "flat curves" of absorption in Puerto Rico 54 students at the University of Puerto Rico§ in whom no history of gastrointestinal disorders was elicited were given a 100 gm. oral glucose-tolerance test. As noted in Table 4, the results are almost identical to those of Moyer and Womack. The military patients in this study had poor absorption of glucose, as demonstrated in the mean values tabulated. The high percentage of normal subjects, in both Texas and Puerto Rico, who showed a limited increase in blood sugar values at the one-half and one-hour periods indicates that this procedure has limited diagnostic value.

D-*Xylose-Tolerance Test.*—Absorption of this pentose by blood levels was evaluated in 14 patients (Fig. 5). There was a marked variation in the range of hourly values among the control subjects and patients. A prolonged slow ascending rise in blood values, as described by Turner[9] in nontropical sprue, was not observed in these patients. Rather, the total absorption appeared to be impaired. The two-hour blood values had most significance in this small series. As more absorption tests were done, the difference in the urinary excretion appeared to be of equal value to blood levels. At the present time, with good kidney function, the five-hour urinary excretion of D-xylose has become the measurement of choice.[19] The specific values before and during ther-

§ These studies were made available through the courtesy of Dr. Fernando M. Monserrate, Director of Student Health Service, University of Puerto Rico.

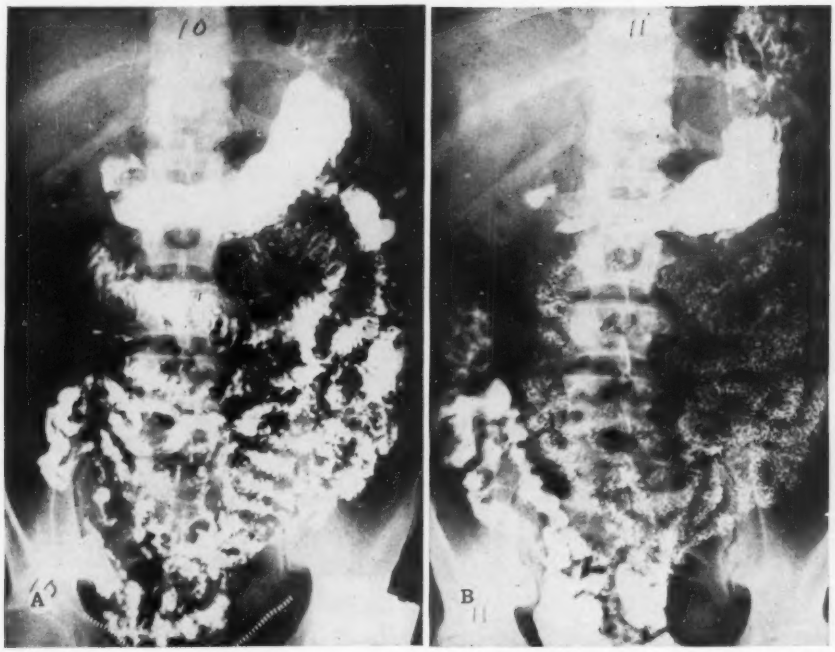

Fig. 3 (Case 4).—*A*, rapid filling of small bowel with small areas of segmentation and irregularities of mucosal folds. *B*, small bowel pattern after four months of oral folic acid therapy. A normal feathery pattern of the mucosal outline is present.

apy are listed in Table 3. The 42 normal subjects had an average of 5.6 gm. of urinary D-xylose (S.D. = ±0.6 gm.). The 19 untreated military patients excreted 2.2 gm. (S.D. = ±1.3 gm.). After therapy, 12 patients studied showed a mean urinary excretion of 4.7 gm. (S.D. = ±0.6 gm.). Most of the patients with a sprue syndrome complain of accentuation of their diarrhea and abdominal complaints after ingestion of the D-xylose. This was an unusual complaint among the normal subjects. The immediate exacerbation of diarrhea and cramps may aid in the diagnosis before the chemical measurement is available.

Vitamin-A-Tolerance Test.—Many workers have felt that the vitamin-A-absorption curve reflects fat absorption. Legerton[20] has presented data to show that the five-hour serum vitamin A value correlates well with fat absorption as determined by a three-day average fecal fat excretion. The mean absorption curve for 32 control subjects is plotted in Figure 6, to compare with the mean absorption curves in military patients before and during treatment. All military patients with this malabsorption syndrome had poor absorption of vitamin A. The fasting vitamin A value for the normal subjects was 42γ per 100 cc. (S.D. = ±13γ). The sprue syndrome patients had an average fasting value of 32γ per 100 cc. (S.D. = ±12γ). Fasting carotenoid values also were moderately depressed in the military patients. The control subjects had fasting mean serum carotenoid values of 120γ per 100 cc. (S.D. = ±56γ), while the military patients had a mean value of 43γ per 100 cc. (S.D. = ±47γ). The depression of the serum carotenoids suggest a prolonged impairment of the absorption of vitamin A precursors.

A striking difference in the serum levels is noted at the fifth and seventh hours. The lower limits of a normal value were defined as 80γ per 100 cc. at five hours and 125γ

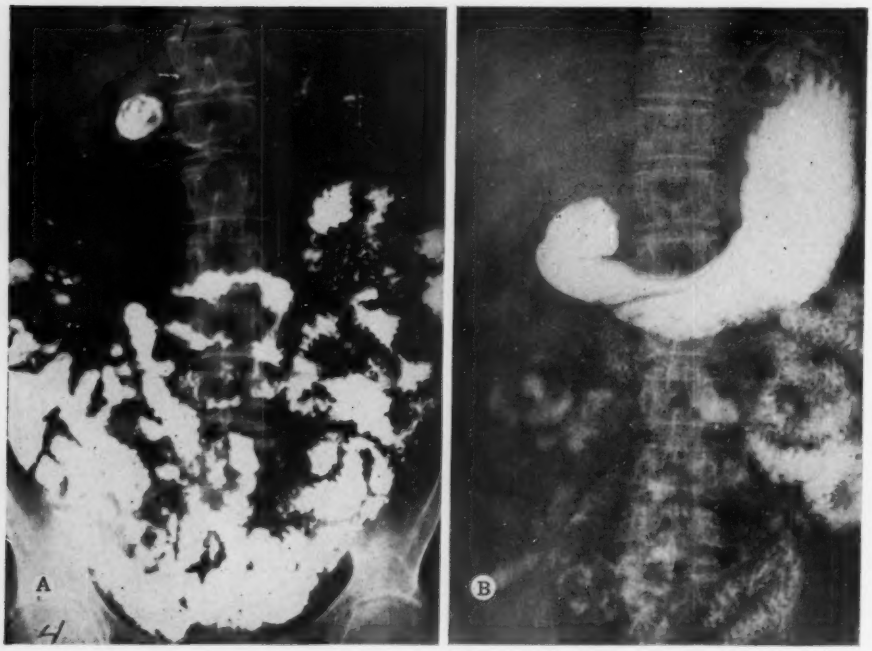

Fig. 4 (Case 13).—*A*, the abnormal segmentation is present in larger aggregates than noted in Figure 3. This type of segmentation was the commonest pattern observed. Some abnormal thickening of mucosal folds is also present. *B*, after five months of oral folic acid therapy a normal small bowel pattern is present.

per 100 cc. at seven hours. In contrast to the "flat" curve before treatment, the marked increase in the standard deviation reflects the improved absorption during treatment with folic acid. Four Puerto Rican patients continued to have a "flat" curve after therapy, indicating a more chronic malabsorption defect. Thirteen patients in this study had daily fecal fat determined. These thirteen patients had poor absorption of vitamin A, although five of them had fecal fat values within normal range. There was no good correlation between the serum vitamin A values and the degree of steatorrhea, when it existed.

Butter-Fat-Tolerance Test.—As noted in Figure 7, the control subjects had a lipemia peak at the third hour followed by a decline in the fifth hour, when the test was terminated. There were wide fluctuations in the values, which probably were associated with the emptying time of the stomach. The patients with malabsorption show a minimal progressive rise during the test period. Serum values with an optical density of 0.1 or greater during the third hour were accepted as evidence of normal fat absorption by this procedure. The most striking comparison is evident during the third hour. However, the shape of the absorption curve was as important as the optical density values. The patients with defective absorption had a progressive increase in lipemia during the five-hour test period. The hourly increments suggest that the total absorption of fat may be normal or only slightly impaired in this disorder. This oral tolerance test, therefore, reflects a change in rate of fat absorption. During folic acid therapy the absorption of fat as measured by lipemia reverted to a relatively normal curve (Fig. 7). Five patients (Puerto Rican) continued to have a "flat" curve similar to the pretreatment observations. Two other patients

TABLE 3.—*Summary Data of Absorbtion Tests of Military Patients*

Case	Oral Tolerance Tests*						Fecal Fat	Duration of Therapy Mo.
	Vitamin A, γ/100 cc.		Urine D-Xylose	Butter Fat, Optical Density			Days, No. / Av. Gm/Day	
	5 Hr.	7 Hr.	Gm./5 Hr.	3 Hr.	4 Hr.	5 Hr.		
1	24 (105)	24 (115)	1.3 (8.2)	---- (0.155)	---- (0.181)	---- (0.055)	12 5.5	7
2	30 ----	70 ----	0.8 ----	---- ----	---- ----	---- ----	13 4.0	7
3	80 (60)	66 (80)	3.1 (2.8)	0.065 (0.031)	0.086 (0.005)	0.036 (0.142)		7
4	---- (230)	---- (340)	---- ----	---- (0.221)	---- (0.091)	---- (0.095)		4
5	5 (82)	5 (59)	2.4 (4.7)	0.017 (0.031)	0.017 (0.000)	0.026 (0.017)		2½
6	50 (40)	80 (90)	1.3 (2.6)	0.036 (0.068)	0.041 (0.070)	0.119 (0.050)	11 8.4	5
7	90 (70)	130 (70)	3.8 (4.8)	0.075 (0.553)	0.096 (0.444)	0.055 (0.251)	11 7.1	5
8	40 (145)	50 (165)	4.9 (3.7)	0.026 (0.091)	0.026 (0.045)	0.060 (0.026)	12 5.8	5
9	55 (170)	60 (265)	2.3 (5.6)	0.045 (0.107)	0.080 (0.142)	0.070 (0.017)	11 2.2	5
10	33 (65)	55 (80)	1.5 (6.4)	0 (0.045)	0 (0.055)	0.086 (0.113)	10 6.3	1½
11	28 (30)	60 (40)	2.3 (2.0)	0.022 (0.180)	0.041 (0.080)	0.119 (0.091)		5
12	14 ----	14 ----	1.0 ----	---- ----	---- ----	---- ----		4
13	50 (125)	50 (110)	2.4 ----	0 ----	0.026 ----	0.013 ----	13 3.8	5
14†	55 (55)	55 (80)	L.B.V. (7.7)	0 ----	0 ----	0.008 ----		None
15	70 (85)	120 (90)	2.4 (4.3)	0.086 (0.004)	0.180 (0.070)	0.200 (0.060)	19 5.0	5
16	40 (70)	40 (85)	2.7 (6.8)	0 (0.065)	0 (0.083)	0.008 (0.045)		2
17	20 (55)	60 (55)	---- (5.4)	0 (0.167)	0 (0.154)	0.0315 (0.091)	11 11.0	5
18	40 (50)	40 (50)	---- (3.1)	---- (0.045)	---- (0.070)	---- (0.045)	17 8.3	10
19	25 (90)	35 (150)	3.6 (8.3)	0.004 (0.022)	0 (0.008)	0 (0.008)	14 7.0	5
20	75 ----	80 ----	2.5 ----	0.113 ----	0.124 ----	0.036 ----		1½
21	60 ----	70 ----	2.3 ----	0.022 ----	0.013 ----	0.004 ----	10 5.6	1½

*Upper figures, before therapy; lower figures, after a period of therapy (when performed).
†L. B. V. indicates low blood values for D-xylose. Urine collection was lost. No therapy was given to this patient at any time.

had a marked improvement in optical density and a normal shape to the curve, although the optical density values at three hours were below the accepted limits for normal subjects.

Fat-Balance Studies.—Six military volunteers who consumed the calculated diet containing 70 gm. of fat had an average daily excretion of 3.5 gm. of fecal fat, with a range of 2.7 to 5.3. This small series confirms the accepted daily normal fecal fat excretion of about 5 gm.[24] Five and one-half grams of daily fecal fat was accepted as the upper limit for normal fat absorption. Only three patients had daily fecal fat values above 8 gm. In view of poor absorption by oral tolerance tests, the degree of steatorrhea was not excessive in any of the patients studied. Five of the thirteen patients had fat excretion of 5.5 gm. or less despite poor

TABLE 4.—*One-Hundred-Gram Oral Glucose-Tolerance Test*

A. Mean blood sugar levels and standard deviation

	Fasting	½ Hr.	1 Hr.	2 Hr.	3 Hr.
Military Patients* (15) Blood sugar, mg./100 cc.	102	114	117	103	102
S. D. †	11	11	20	17	15
University of Puerto Rico Students (54) Blood sugar, mg./100 cc.	122	172	153	135	122
S. D.	17	32	34	29	23
Moyer & Womack [18] (103) Blood sugar, mg./100 cc.	96	145	128	96	82
S. D.	11	25	30	15	16

B. Percentage of normal volunteer subjects showing less than a 25 mg./100cc. and 40 mg./100cc. increment in blood sugar values at one-half and one hour

	University of Puerto Rico Students, %	Subjects of Moyer & Womack, [18] %
Less than 25 mg./100 cc. at 1/2 hr.	22	20
Less than 40 mg./100 cc. at 1/2 hr.	45	40
Less than 25 mg./100 cc. at 1 hr.	45	45
Less than 40 mg./100 cc. at 1 hr.	65	65

* Figures in parentheses are the number of patients studied.
† S. D. indicates standard deviation.

TABLE 5.—*Comparison of Serum Iron Levels After Oral Iron Tolerance Test**

	Serum Iron		
	Fasting, γ/100 Cc.	0 to 40 γ/100 Cc. Increment, % of Patients	40 γ/100Cc. or Greater Increment, % of Patients
Normal patients (28)	76 (S. D. ± 28)	28	72
Sprue syndrome patients (13)	75 (S. D. ± 14)	69	31

* A larger percentage of normal patients have a greater serum iron increment than that observed in the sprue syndrome patients after an oral dose of ferrous sulfate. Fasting serum values are similar in the two groups of patients studied. One standard deviation is listed for the fasting serum iron values.

absorption of vitamin A and butter fat. No fat-balance diet programs were done during folic acid therapy. The average daily values for all patients are listed in Table 3.

Iron Absorption.—Fasting serum iron values were determined in 28 control subjects and 13 patients with the sprue syndrome. Fasting serum iron values were similar in the two groups. Hypoferremia was not present in the sprue syndrome patients. No particular type of absorption curve could be detected by observation of the hourly serum iron values. By inspection, the absorption patterns could be divided into two groups: namely, patients who showed more and those who showed less than a 40γ per 100 cc. increase in serum iron during the absorption period tested. In Table 5 the percentages of patients are given. In the absence of hypoferremia in the sprue patient, one may assume that the clearance rate of absorbed iron from the plasma is similar in the two groups. This technique of measurement is a poor index of iron absorption and represents only an estimation. However, the results are suggestive that iron is poorly absorbed. Similar results have been noted by Badenoch and Callender [22] in idiopathic steatorrhea.

Response to Specific Therapy.—This study was initiated to determine whether a malabsorption syndrome similar to the type observed in the Far East exists in this area. Efforts have been made to contact patients after discharge from the hospital. During the early phase of the study the patients received 15 mg. orally of folic acid daily and 30γ of cyanocobalamin intramuscularly twice weekly. The cyanocobalamin levels from eight patients were determined before treatment. After a few months the reported serum values demonstrated that these military patients before treatment had a mean cyanocobalamin level of 153μγ/ml. of serum, with a range of 80μγ to 244μγ/ml. Eighteen control subjects had a mean concentration of 219μγ/ml. with a range of 85μγ to 404μγ/ml. ‖When it was evident that no deficiency of cyanocobalamin, as measured by serum levels, existed, only folic acid therapy was prescribed. In this group of patients without anemia there is no impairment of the clinical response if cyanocobalamin is omitted from therapy. One medical officer (Case 14) who desired to lose weight did not accept therapy. It was of interest to note that he gradually had a

‖ These determinations were done by Dr. Marion Beard, in Louisville, Ky. The normal serum cyanocobalamin values in his laboratory have a range of 8μγ to 460 μγ/ml., with a mean value of 200μγ/ml.

remission of his syndrome over a three-month period. However, the patient followed a high-protein low-fat diet which was used successfully for such patients by military authorities in India during World War II.

During the therapy most patients noted an improvement in appetite associated with gradual cessation of their diarrhea. However, the change in bowel habits was not prompt and most patients required two to three weeks to see marked lessening of stool frequency. Some patients continued to have intermittent mushy stools, even though they regained weight and lost the feeling of weakness and anorexia. Certainly, the poorest improvement was observed among the Puerto Rican soldiers. Three patients (Cases 6, 7, and 11) had little or no weight gain. There was improvement in the frequency of diarrhea, but intermittent episodes persisted. These patients have been given small doses of cortisone acetate (50 to 75 mg. daily), without noticeable improvement.

No effort was made to outline a specific diet for these patients. It was important to know if the patient could return to a regular army mess. However, some limitations in fat intake were evident, either from past intolerance before treatment or indoctrination while under observation in the hospital. Patients were given no instructions on discharge from study except to abstain from alcohol. Numerous patients did indulge in use of beer and rum and reported that they could not tolerate alcoholic beverages as they did before onset of symptoms.

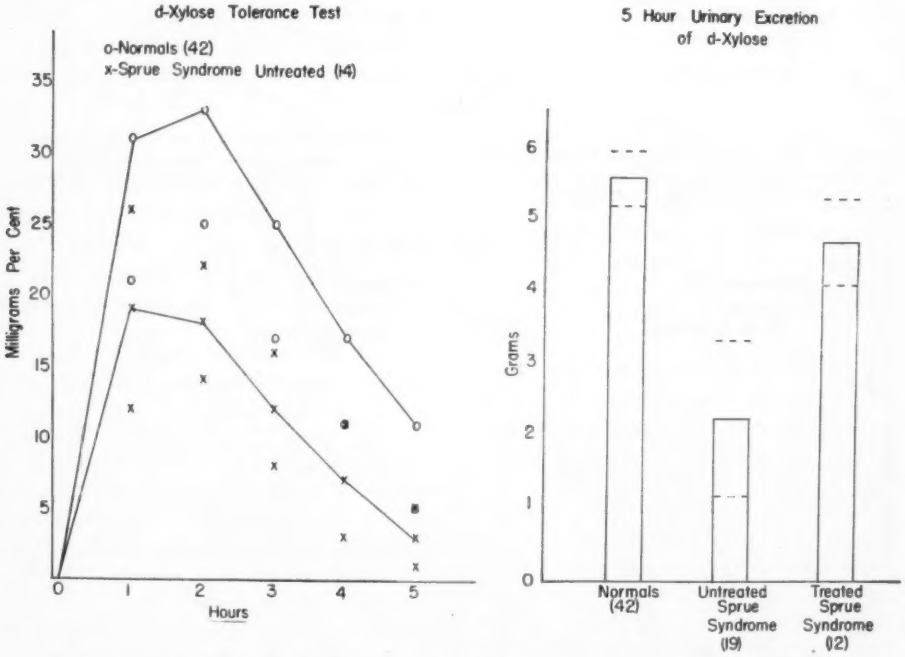

Fig. 5.—The mean blood values for the tolerance tests are plotted by the continuous lines. The range of a standard deviation is marked for each hour. Only the lower values of the standard deviation for the normal subjects are plotted. The two-hour blood level is the most diagnostic value to determine. The five-hour urinary excretion of D-xylose is depressed in the military patients before treatment. The urinary excretion has improved during folic acid therapy, although the slight impairment may be associated with the time period after therapy. Figures in parentheses after each group indicate the number of patients studied. Dotted lines on bar graph indicate standard deviation of urinary excretion.

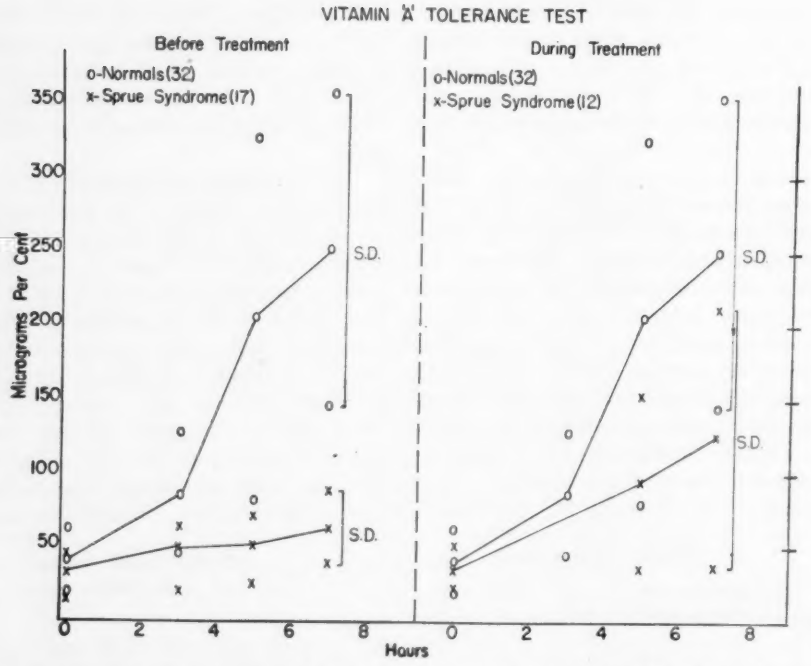

Fig. 6.—The mean values for the serum levels of vitamin A are plotted by the continuous line. The range of a standard deviation is marked at each determination. There is progressive improvement in the absorption of vitamin A during folic acid therapy. Figures in parentheses indicate the number of patients studied.

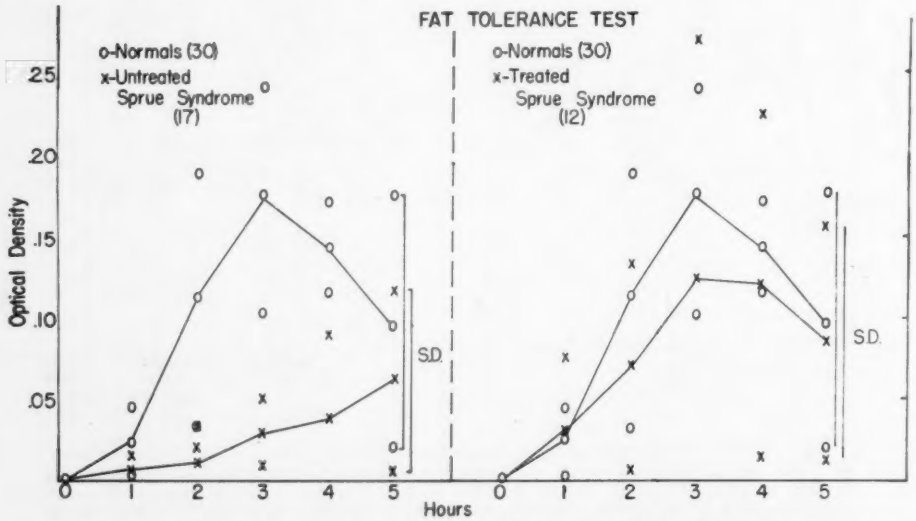

Fig. 7.—The plotted curves are the mean values of serum lipemia for each group after the ingestion of 30 gm. of butter fat. The values for a standard deviation are plotted for each determination. The figures in parentheses indicate the number of patients studied. The absorption of butter fat is relatively normal during folic acid therapy.

Ten of the patients lived with their families and consumed a home diet no different from their accustomed diet in the United States. It is therefore difficult to establish any dietary deficiency or monotony of diet as an etiologic factor in this syndrome.

Comment

The present preliminary study indicates that a gastrointestinal malabsorption syndrome does exist in Puerto Rico. The observed patients were seen in an early phase of diarrhea without marked secondary vitamin-deficiency signs. The fasting values of serum vitamin A, carotenoids, iron, and cyanocobalamin in this small series confirm the clinical observations that the patients were seen in a very early phase of malabsorption. The symptoms described fit somewhat into the first stage of sprue as defined by Stefanini[4] and Elder.[5] Likewise, the term "incomplete sprues" of Manson-Bahr and Willoughby[23] could apply to this group. In Puerto Rico the symptoms were of shorter duration, and progression to deficiency states, especially glossitis, was not present at the time the patients were studied.

The climatic stability of Puerto Rico throughout the year does not lend support to seasonal incidence of the disease, and patients continued to be observed throughout the year. Although the syndrome has not been diagnosed previously among military personnel in Puerto Rico, there is no evidence to suggest that this is a recent problem. In retrospect, these symptoms have been observed and treated with vitamin therapy without definition. Tropical sprue in Puerto Rico in the past has always been associated with a macrocytic anemia. None of the patients in this small series was anemic. As evidence has accumulated to define a malabsorption syndrome without anemia, a few cases have been observed in the native population. In all probability a large number of patients in Puerto Rico could be found in this category with the realization that gastrointestinal dysfunction can exist without anemia. It is important to emphasize that no history of dietary alterations could be elicited. Military personnel from the United States had identical dietary habits in Puerto Rico. Excellent mess and commissary facilities have allowed a varied diet, especially with the present abundance of frozen meats, vegetables, and fruits. Patients were fed in the Army mess with a balanced diet menu. Puerto Rican personnel at home used lard (animal fat) for cooking, while military patients from the states have used, for the most part, vegetable oils. None of the patients had enteric pathogens found by stool culture. However, the standard procedures for isolation of Shigella and Eberthella organisms do not exclude the possibility that bacterial flora changes are responsible for the symptoms.

Limited studies of small bowel x-ray changes have been reported in tropical sprue syndromes.¶ Suarez has stated that 70% of 71 cases of tropical sprue studied in Puerto Rico had evidence of deficiency pattern. These cases had megaloblastic bone marrow changes with macrocytic anemia, in contrast to this present military group without anemia. Seventeen (80%) of the present series had abnormal x-ray studies. In the present study there was no good correlation between the initial x-ray examination and the oral tolerance tests. It will be noted that four patients had no abnormalities in the small bowel pattern described, despite the presence of impaired oral absorption of butter fat, vitamin A, glucose, and D-xylose. In fact, one patient showing the second highest fecal fat excretion for the 10-day test period had minimal segmentation changes in the small bowel. Possibly in these patients more frequent x-ray studies would have demonstrated transient changes. Frequent fluoroscopy may be necessary to see transient changes in segmentation and coarsening of the small bowel pattern. For the most part, the x-ray studies have shown abnormalities, and the procedure may be considered of diagnostic value when this facility for study is available. When com-

¶ References 1 and 17.

pared with the oral tolerance tests, the results would indicate that absorption defects may be present in the absence of changes found by x-ray studies as performed in this group of patients.

Patients who had abnormal small bowel patterns showed a tendency to revert to normal pattern or show improvement after they had received folic acid therapy. Even patients who had received treatment for a period of only two months showed correction of the thickened folds and segmentation. Preliminary studies[24] have indicated in the untreated sprue patient a decrease in the dissolved mucoprotein fraction of the succus entericus as measured by the procedure of Jerzy Glass and Boyd.[25] No studies were done after therapy to determine whether such an abnormality persisted. However, these abnormal changes may be associated with the reaction of the barium suspension with mucus to produce the classical segmentation and appearance of thickened folds.

Four oral tolerance tests have been used to evaluate absorption in the military patients. When compared with the results in control patients, they have appeared useful in diagnosis of malabsorption in the small bowel. The glucose-tolerance test, as observed in this area, revealed numerous control subjects who had a minimal rise in blood glucose values. The marked variation with this test has suggested that D-xylose be used, since the urinary excretion can be measured without the need for ventipunctures. Similar variability of results has been noted by Cooke[26] in the study of idiopathic steatorrhea. If information regarding glucose absorption is desired, the results of the intraduodenal drip method described by Frazer appears to be more reproducible.[27] Other oral tolerance tests with aminoacetic acid (glycine), folic acid, 3-methylglucose and radioactive cobalt (Co^{60}), cyanocobalamin are in progress. Preliminary results do not indicate that they aid in further diagnosis of this disorder.

Despite the poor oral absorption of vitamin A and butter fat before treatment, the fecal fat excretion in the patients was only moderately elevated; two patients had a daily excretion above 8 gm. In the early phase of intestinal malabsorption the "stress" loading of the oral tolerance test for butter fat and vitamin A showed more impairment over a short period of time (5 hours) than was observed by 24-hour fat-balance data. Only limited conclusions of poor fat absorption can be made from these tolerance tests in view of the minimal steatorrhea observed. These differences may be associated with absorption of short-chain fatty acids directly into the portal circulation. These short period tests only indicate impaired ability of the bowel to handle fat rapidly. The impairment of fat absorption indicated by vitamin A and butter-fat tests over a short period of time does not reflect the total absorption capacity of the bowel in a 24-hour period. The butter fat at 5 hours showed a slow progressive rise, which meant good absorption in a 24-hour period for those patients who had less than 5.5 gm. of daily fecal fat. Two-thirds of the dietary fat was from milk and butter. These observations probably should be expected when patients are evaluated early. Using different procedures, Elder[5] noted that 40% of 400 cases of tropical sprue in India among British troops had normal fecal fat values. Likewise, Keele and Bound[6] reported normal fecal fat excretions in 20% of 600 cases. Most of the British reports emphasize an almost universal occurrence of glossitis, which suggests that the malabsorption defect has been associated with more nutritional deficiencies than has been noted in Puerto Rico. Hence, one might have anticipated that excessive steatorrhea would not be prevalent in this study. Possibly a more complete defect could be observed if these patients had a fat source with longer-chain fatty acids. However, the diet was selected to conform with the eating habits of this group. It is rather difficult to attribute weight loss to this minimal increase in fecal fat. Rather, the general response of the patient with anorexia, nausea, and abdom-

inal cramps probably limits the total caloric intake.

The response to folic acid therapy has been gratifying, but this therapy is not a complete answer. The majority of patients showed improvement in the x-ray studies of the small bowel and the oral tolerance tests. No control or regulation of dietary habits was made. The patients returned to military duty and continued to receive oral folic acid. Possibly further improvement could have been obtained if low-fat high-protein diets had been prescribed. However, it is important to note that the disease did not progress and patients were improved without such food restrictions. Many patients have tolerated fried fatty foods without distress. These observations confirm the opinion in Puerto Rico that the young patient responds better to therapy than the older person. Rodriguez-Molina[3] has emphasized that many young patients with tropical sprue associated with macrocytic anemia in Puerto Rico remained well after short periods of liver-extract therapy. Woodruff[28] evaluated 34 patients with tropical sprue in India at a two- to three-year period after they had returned to England. All were able to work, and only three patients were not considered well. One may anticipate that these observations will be repeated with wider recognition of the syndrome.

At the moment there is no adequate explanation for the etiology of the sprue syndrome. Although temperature readings tend to be higher throughout the year, there are in Puerto Rico no marked seasonal changes with rain to be associated with an increase in the frequency of diarrheas, as noted in India.[4] The patient in Puerto Rico had good dietary habits. Bacterial pathogens and parasites are not evident from routine laboratory studies. Aspiration of the small bowel juice in the jejunum has shown no bacterial growth in sprue patients differing from that of normal volunteers.# Therefore, at present no explanation can be given for this malabsorption syndrome.

Nadel, H., and Gardner, F. H.: To be published.

Summary

A malabsorption syndrome has been observed in military personnel stationed in Puerto Rico, characterized by weight loss, diarrhea, dyspepsia, and lassitude. None of the patients were anemic. Laboratory studies have indicated poor absorption of glucose, D-xylose, vitamin A, and butter fat. The majority of patients responded well to oral folic acid therapy.

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Chronic Benign Residuals of Coccidioidomycosis

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and
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Coccidioidomycosis is usually an acute relatively mild, self-limited illness. However, a very few cases progress to the highly fatal disseminated phase of the disease. Another small per cent show persistent pulmonary residuals without dissemination, which are mostly asymptomatic. This is a regional disease. However, with rapid transportation readily available to the public and with large numbers of military personnel having been trained and stationed in endemic areas during and following World War II, physicians throughout the United States might expect to encounter these pulmonary residuals. Failure to recognize these lesions often results in the making of an incorrect diagnosis of tuberculosis or other serious pulmonary disease, with the institution of prolonged ill-advised therapeutic measures and the imposition of considerable hardship on the patient. Therefore, it is important for all physicians in the United States to be aware of the diagnostic features and the prognostic implications of these residual pulmonary lesions. Although these chronic coccidioidomycotic lesions are described in medical literature,* a further description with full emphasis on available diagnostic tools is felt to be timely. This report is based on our experience in 50 cases of chronic benign pulmonary residuals due to coccidioidomycosis.

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* References 1-3.

Definition and Description of Lesions

The term "chronic benign residual" will be used to describe any pulmonary lesion persisting three or more months after acute pulmonary coccidioidomycosis or otherwise demonstrated to be coccidioidal in origin without evidence of dissemination. The following types of lesions were observed:

Pulmonary cavitation	21
Nodular densities, single or multiple, with or without calcification	27
Pleural effusion	2
Fibrosis	2
Infiltrative lesions	2

More than one type of sequela can occur in any single case. This was demonstrated well in one patient who had pleural effusion complicating cavitation. Residual lesions were observed in 13 cases following the clinical manifestations of acute coccidioidomycosis. Pulmonary lesions were found in 34 patients on routine chest x-rays or during studies for other disease. The other three patients were examined because of chest pain or hemoptysis. In only 11 of these 37 persons were there past histories of illnesses compatible with acute coccidioidomycosis. It is therefore apparent that three-quarters of the cases will present problems in the identification of pulmonary lesions.

Diagnosis of Residual Coccidioidal Lesions

A history of exposure is essential to the diagnosis of coccidioidomycosis. This will usually entail residence in an endemic area or at least passage through such an area. Rarely is laboratory exposure or the handling of contaminated objects from an

endemic area an important factor. The endemic areas in the United States are in the southern portion of California, notably in the San Joaquin Valley; the southern part of Arizona and New Mexico, and the southwestern portion of Texas.

The coccidioidin skin test will practically always be positive in the presence of chronic benign residual coccidioidomycosis. The test is performed by injecting 0.1 cc. of a 1:100 dilution of coccidioidin skin testing antigen intradermally and interpreting the reaction in 48 hours. A negative reaction in the presence of a suspicious lesion should be repeated with a 1:10 dilution. The criteria for positive reactions are identical with those for tuberculin tests. Smith[1] found only 10 negative skin reactions in 235 cases of coccidioidal cavitation, in 7 of which the subjects had been tested with the 1:100 dilution only. One should consult his reports for excellent detailed information on the uses and significance of the coccidioidin skin test.[4] In the present series there were 47 positive and 1 negative skin reactions. The latter subject had been reported to have a positive reaction when tested previously elsewhere. Since tuberculosis and other mycotic diseases must often be excluded, tuberculin, and, in appropriate cases, histoplasmin and blastomycin skin tests should be applied. If the latter tests are negative and the coccidioidin reaction is positive in the case of a suspicious lesion, the diagnosis of coccidioidomycosis may be made with reasonable accuracy. The coccidioidin skin test almost always becomes positive by the fourth week after the initial infection. The positive test implies that there is chronic coccidioidal granulomatous tissue present in the patient. Multiple skin tests were initiated in 39 cases, of which 22 showed only a positive coccidioidin test. In only 10 cases was it necessary to make the diagnosis on the history plus skin sensitivity, since additional evidence of coccidioidomycosis was present in the remainder.

Serologic tests are quite valuable in establishing etiology. In this phase of investigation Smith has made many important contributions.[5] His laboratory performed all serological studies on our cases. Precipitins appear relatively early in the course of acute infection and usually disappear within three months. Thus, by the time a chronic benign coccidioidal lesion is discovered the precipitin test is usually negative. Complement-fixing antibodies develop somewhat later than do precipitins and persist for a longer period of time. The maximum titer will almost always be low (1:32 or less) in the presence of benign residuals, in contrast to the higher titers often found in the disseminated form of the disease. However, negative serological tests do not eliminate the diagnosis of chronic coccidioidal infection, since approximately 60% of cases with coccidioidal cavities fail to demonstrate a positive serological reaction.

Culture of Coccidioides immitis or microscopic identification of the organism proves the diagnosis. Sputum and gastric washings will produce a surprisingly high percentage of positive cultures from cavitary lesions. Smith was able to culture C. immitis in 40% of 274 coccidioidal cavities.[1] In the 16 of our cases with cavitation in which cultures were attempted, 6 positive cultures were obtained. All efforts to culture the organism from sputum or gastric washings were unsuccessful in patients with chronic infiltrative, fibrotic, or nodular lesions. In such cases the history, skin test, and serological studies must be relied upon for the diagnosis. Excision biopsy may be necessary in some cases.

Report of Case

CASE 1.—A 31-year-old male officer was admitted to the hospital on Dec. 15, 1952, because of a pulmonary infiltration in the left apex, found on routine chest x-ray. He complained only of easy fatigability. He was a native of the San Joaquin Valley. Late in October, 1952, he made an inspection of an Army installation in an endemic area. On Nov. 12, 1952, he developed a febrile illness with chills and slightly productive cough. Chest x-ray was reported as normal. He was treated with chlortetracycline (Aureomycin), and symptoms subsided in about one week. During the next three weeks his weight dropped from 186

lb. (83.7 kg.) to 168 lb. (75.6 kg.) Physical examination revealed dullness and increased fremitus over the left upper chest and moist rales over the left apex posteriorly. He was afebrile throughout hospitalization. Complete hemogram was normal; erythrocyte sedimentation rate was 23 mm. in an hour. Chest x-ray Dec. 17, 1952, showed an infiltrative lesion involving the left apex, best observed on lordotic view (Fig. 1A). Coccidioi-

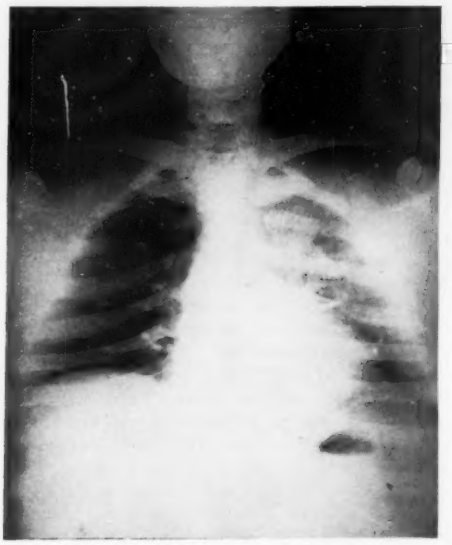

Fig. 1A.—Dec. 17, 1952. Infiltration in left apex. Sedimentation rate 23 mm. in an hour. Complement-fixation titer 1:8.

din, 1:100, and first strength PPD tests were positive. Repeated cultures of gastric washings for tubercle bacilli and fungi were negative. Coccidioidal precipitin test was negative, but the serum complement fixation was positive to a titer of 1:8. Serial x-rays showed gradual but incomplete clearing in the left apex during four months' subsequent hospitalization (Fig. 1B). The sedimentation rate returned to normal in six weeks. The serum complement-fixation titers rose to a maximum titer of 1:64 on March 9, 1952, but had dropped to a titer of 1:32 on April 20, 1952. When the patient was last observed, on Nov. 18, 1952 (approximately one year after onset), the complement-fixation titer was 1:16, with incomplete clearing of the infiltration in the left apex (Fig. 1C). He was completely asymptomatic.

Comment.—This person undoubtedly had unrecognized acute primary coccidioidal pneumonitis in November, 1952. The history of a recent visit into a coccidioidal area,

Fig. 1B.—April 20, 1953. Partial clearing of left apical infiltrate. Sedimentation rate 8 mm. in an hour. Complement-fixation titer 1:32.

lack of fever and other constitutional symptoms, the positive skin test, the failure to culture acid-fast bacilli, the rapid decrease in the sedimentation rate, and, lastly, the

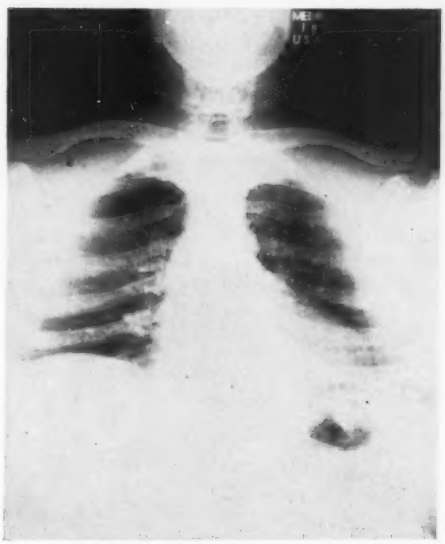

Fig. 1C.—Nov. 18, 1953. Further clearing of left apical infiltration. Complement-fixation titer 1:16.

changing complement-fixation titers pointed to a diagnosis of coccidioidomycosis. If this diagnosis had not been considered, the patient might well have been subjected to therapy for tuberculosis with prolonged hospitalization. In this instance the precipitin test was negative when first observed, five weeks after onset. This case illustrates the persistence of pulmonary infiltration and complement-fixing antibodies for one year and the value of serial serological tests when cultures are negative.

Case 2.—A 27-year-old Air Force officer was assigned to an air base in the San Joaquin Valley during 1945 and 1946. He recalled an episode of coryza with a productive cough in that period lasting approximately 10 days. Again in 1947 he spent several months in the San Joaquin Valley. Later he was assigned to Okinawa, where he had an undiagnosed illness with a 12 lb. (5.4 kg.) weight loss. Chest x-ray apparently was normal. During a routine physical examination in March, 1950, a chest x-ray showed a thin-walled cavity in the left upper lung field. No additional studies were made, and the patient flew fighter missions in Korea until he returned to the United States in August, 1951. He was hospitalized for study two months later. He was asymptomatic, and physical examination was essentially normal. The erythrocyte sedimentation rate was normal. PPD second strength was negative; coccidioidin 1:100 was positive; precipitin test was negative, and the complement fixation was positive in 1:2 titer. Repeated cultures of gastric washings failed to grow acid-fast bacilli, but a gastric specimen cultured C. immitis. Chest x-ray showed a thin-walled cavity in the region of the left second anterior rib (Fig. 2). The patient was returned to duty to be followed with periodic chest x-rays.

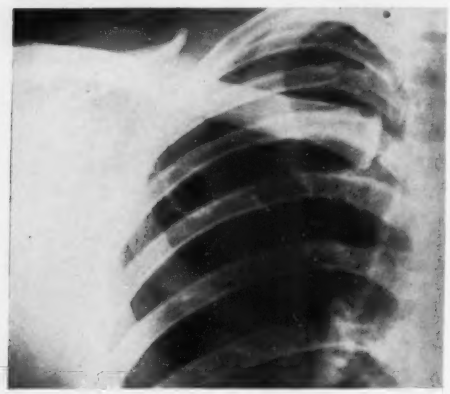

Fig. 2 (Case 2).—Thin-walled, cyst-like cavity in right upper lung, present unchanged for at least one and a half years.

Comment.—This case illustrates the benign nature of the "typical" thin-walled coccidioidal cavity characterized by minimal surrounding reaction. This officer served as a combat pilot for almost one and one-half years between the time of the initial discovery of the cavity and hospitalization, without apparent change in the chest lesion or physical harm to the patient. The importance of cultures in establishing a definite etiology is emphasized.

Case 3.—A 28-year-old woman had resided almost her entire life in the San Joaquin Valley. In March, 1951, she became ill, with cough, afternoon fever, malaise, and easy fatigability, followed two tweeks later by typical lesions of erythema nodosum. The chest x-ray then showed thickening of the right interlobar fissure. In October, 1951, a "suspicious" lesion in the right midlung field was reported. Coccidioidin and PPD skin tests were reported as positive. She entered the hospital in December, 1951, with an apparent extension of the chest lesion on x-ray and with a cough productive of blood-streaked sputum. The physical examination was essentially normal. Chest x-ray revealed a 2 cm. cavity in the apical segment of the right lower lobe, with streaks of increased density extending toward the hilum (Fig. 3). The hemogram was normal, with the erythrocyte sedimentation rate varying from 24 to 32 mm. in an hour. Tests of second strength PPD and coccidioidin 1:100 were positive. Repeated cultures of gastric washings and sputum were negative for fungi and acid-fast bacilli. The coccidioidal complement fixation was positive in a titer of 1:4.

The patient remained asymptomatic, and no changes were seen in serial x-rays until early February, 1952. She then developed right shoulder pain, followed shortly by signs and symptoms of right pleural effusion. This regressed spontaneously by March 27, 1952. Cultures of pleural fluid for acid-fast bacilli and fungi were negative. Chest x-rays dated April 25, 1952, showed pleural thickening without definite evidence of fluid or cavitation. The patient was pregnant and delivered a normal baby without complications in September, 1952. Chest x-ray then showed a linear density at the site of the previous cavity. There was no change in the x-ray until July, 1953, when again a cavity was noted in the right midlung field (Fig. 3). Coccidioidal complement fixation titer was 1:4. She was asymptomatic. The cultures of gastric washings were again negative for both fungi and acid-fast bacilli. Surgery was considered but

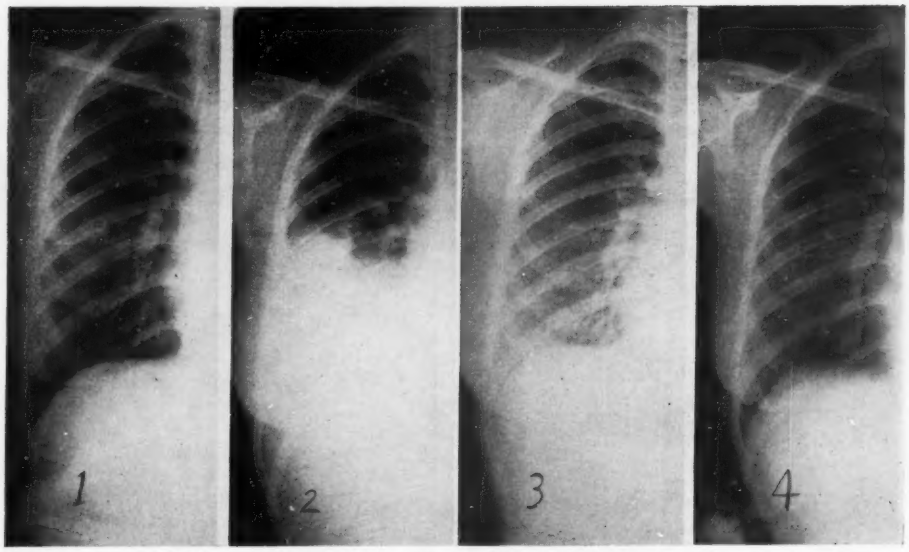

Fig. 3 (Case 3).—(*1*) Dec. 18, 1951; cavity in apical segment of right lower lobe, with strands of density radiating to hmilum. (*2*) Feb. 11, 1952; pleural effusion at maximum. (*3*) April 25, 1952; pleural effusion has absorbed, with residual pleural thickening. (*4*) July 31, 1953; lung field clear; cavity has reappeared.

was later deferred, as the cavity again decreased in size. The last x-ray was in July, 1955, and showed further reduction in the size of the cavity. The patient continued in excellent general health.

Comment.—The occurrence of hydrothorax or pyopneumothorax was noted by Smith[1] in about 5% of his cases of coccidioidal cavitation, and C. immitis was cultured from the pleural fluids in each instance. In the present case all cultures from sputum, gastric washings, and pleural fluid were negative. This patient was observed for almost four years, during which time a cavity appeared; pleural effusion developed, with subsequent closure of the cavity; the cavity reappeared, and later it regressed. This apparently does not represent reactivation or dissemination of the disease, as there was no change in the complement-fixation titers and she remained symptom-free. It is considered proper at present to continue with conservative therapy in this type of case.

Case 4.—A 26-year-old soldier of Mexican extraction was admitted to an army hospital in October, 1952, for evaluation of an old eye injury. Routine admission chest x-ray showed a solitary "coin" lesion near the periphery in the second left anterior interspace. Previous chest x-rays in 1951 were normal. The patient had lived in endemic areas in 1944 and again in 1951. Immediately prior to this present hospitalization the patient was stationed for a period of five months in southern Arizona. There he had no acute respiratory infections. Physical examination was essentially normal. The hemogram and erythrocyte sedimentation rate were normal. PPD and coccidioidin skin tests 1:100 were positive. The lesion was excised by wedge resection. Grossly it had a fibrous covering, with central caseation. Microscopically the wall consisted of granulomatous tissue. Distributed throughout the caseous material were numerous ovoid capsules, most of which were empty but a few of which contained endospores. The culture of the surgical specimen grew the typical mycelia of C. immitis.

Comment.—Preoperatively the "coin" lesion was considered most likely to be a tuberculoma. The subsequent culture left no doubt as to the etiology of the "coin" lesion.

Case 5.—A 32-year-old soldier was admitted to the hospital on May 20, 1948, with a four-day history of fever, chest pain, dyspnea, and general malaise. He had failed to respond to antibiotics as an outpatient. The patient had visited southern Arizona two weeks prior to the onset of the

present symptoms. On admission the temperature was 100 F and there were paroxysms of coughing. Rales and rhonchi were heard throughout the lungs. A confluent urticarial rash was seen over the back, hips, and axillae. The chest x-ray showed multiple confluent patchy densities through both lung fields (Fig. 4A). Sputum cultures and

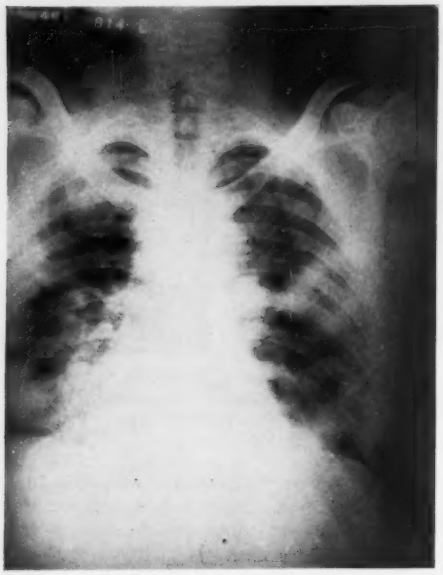

Fig. 4A (Case 5).—May 21, 1948. Acute coccidioidal pneumonia, with multiple confluent and patchy densities.

guinea pig testicle innoculation were positive for C. immitis. The white blood cell count was 11,700, with a normal differential count. The coccidioidal precipitin test was positive. The patient had a remittent fever to 103 F for seven days, and then low-grade fever (99 to 100 F) for four weeks. There was marked symptomatic improvement in 10 days, after which only a slight nonproductive cough remained. The white cell count reached a maximum on the 10th hospital day, of 17,750. Five to ten per cent eosinophiles were present from the 7th to the 25th hospital day. Chest x-rays showed progressive clearing until the third week and then remained unchanged until the time of discharge from the hospital, in November, 1948 (Fig. 4B). This patient has remained in good health and on active duty. The last x-ray, in December, 1952, showed some decrease in size and increase in the density of the multiple nodular residuals (Fig. 4C).

Comment.—This case illustrates many features of the acute phase of coccidioido-

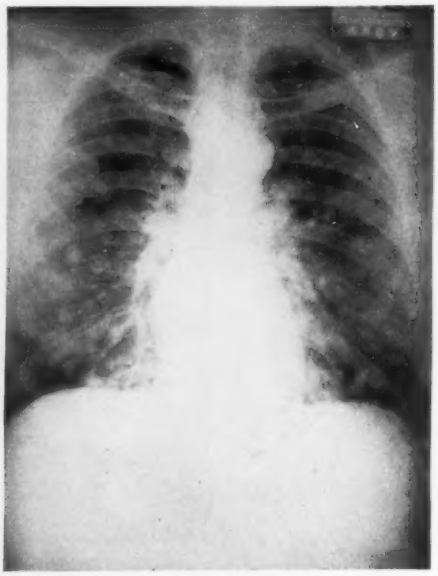

Fig. 4B (Case 5).—Nov. 4, 1948. Multiple nodular residuals six months after primary coccidioidomycosis.

Fig. 4C (Case 5).—December, 1952. Slight decrease in size and "hardening" of nodular residual lesions, four and one-half years after primary disease.

mycosis with the formation of multiple nodular residuals. Without the previous history, the x-rays would be suggestive of a metastatic carinoma. The benignity of these lesions is well demonstrated in this patient, who was living a vigorous life four and a half years after his primary infection.

CASE 6.—A 26-year-old W.A.C. had worked in a tuberculosis sanitarium in 1948 and 1949. She resided in the San Joaquin Valley at Madera, Calif. She was stationed at Fort Belvoir, Va., in December, 1951, when she developed a "bad cold." A chest x-ray showed "spots on the lungs." During a furlough at her home, in Utah, in March, 1952, she developed symptoms of fatigue, night sweats without fever, and chest pain. This necessitated hospitalization at an Air Force Base, from whence she was transferred to this hospital. A physical examination was essentially normal. The white cell count was 22,600, with a normal differential count. Erythrocyte sedimentation rate was 24 mm. in an hour. Chest x-ray showed a nodular density with calcification in the right mid-lung field and two nodular densities adjacent to the heart shadow on the left, one of which showed central calcification (Fig. 5). PPD test was negative, and test with coccidioidin 1:100 was positive. Serological tests for coccidioides were negative. Repeated culture of gastric washings failed to grow acid-fast bacilli. The patient was afebrile and asymptomatic in the hospital and was discharged 10 days after admission.

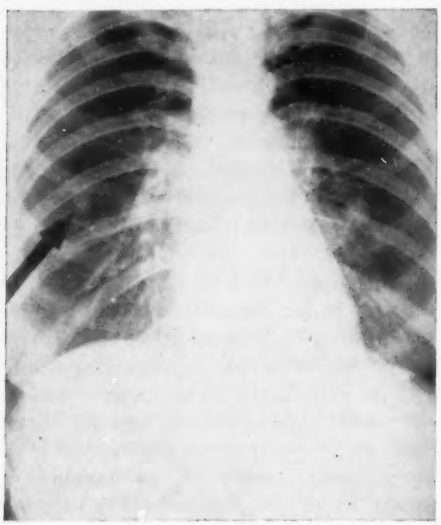

Fig. 5 (Case 6).—There is a nodular density with central calcification at the anterior end of the right fourth rib. Two similar nodular densities project beyond the heart shadow on the left in the fourth anterior interspace, with calcification in the smaller of the two shadows.

Comment.—In view of the results of the skin tests, tuberculosis was considered unlikely and coccidioidomycosis most probably the diagnosis. Histoplasmosis was not ruled out, but there was no history of residence in known endemic areas. The presence of calcification tended to eliminate Boeck's sarcoid. It was felt that the calcified pulmonary lesions were not related to her respiratory symptoms of December, 1951, but rather a residual of a remote infection. The residence in a coccidioidal endemic area two years earlier suggested the diagnosis of coccidioidomycosis.

General Comment

These cases were characterized by a paucity of symptoms and a benign course. There were no symptoms referable to the residual pulmonary lesions in 32 of our 50 patients. In the symptomatic patients the most frequent complaints were of slight cough, weakness, and fatigability. Seven patients reported production of blood-streaked sputum, but this was confirmed in only four upon hospitalization. Hemoptysis was minimal and intermittent in all cases. One person told of hemoptysis of a half cupful of bright red blood, but on observation only minimal blood streaking was observed. There was one case with multiple nodules with mild shortness of breath. The complaints of cough and fatigue were in most cases probably not the result of the observed coccidioidal pulmonary residuals. Only 14 of these cases were observed for more than one year (average, 3.3 years after discovery); thus no accurate long-term evaluation can be made concerning these lesions. The only serious complications in this group was the occurrence of pleural effusion in one case. This patient (Case 3) is clinically well three and a half years after pleural effusion secondary to cavitation, although the cavity is still present. The 14 patients with known coccidioidal residuals for 1 to 10 years are all alive and apparently

healthy. Two cavities were observed to close in two to four months, with residual fibrosis in one. Winn[6] was able to follow closely 92 cases with cavitation for approximately five years. In 25% the cavities closed spontaneously, with nodular residuals in 6%; 20% closed after simple collapse procedures, and 10% persisted without harm to the patient. Similar results were reported by Jamison[2] in his 35 cases observed for 1 to 18 months, with 16 cavities closing, 6 with nodular residuals. The optomistic view is not confirmed by all authors. Joress and Busheuff[7] cautioned that "reactivation" of apparently innocuous residual lesions may produce "focal or disseminated pathological activity." In support of this concept they cite 4 cases in their series of 23 observed at a veterans administration hospital. Three had hemoptysis due to cavitary lesions, of sufficient magnitude to warrant surgery in two of them. The fourth case in this report was believed to have developed disseminated disease from chronic pulmonary residuals. However, the case history suggests that dissemination had occurred shortly after the initial infection some three years earlier. We have been able to find reports of only two cases in which dissemination occurred in the presence of an apparently benign coccidioidal residual. One patient[8] had a thin-walled cavity and developed a facial lesion more than a year after leaving an endemic area. The facial lesion healed completely under antibiotic and roentgen therapy. The other patient[9] also had a coccidioidal cavity and developed a "pimple" on the shoulder from which C. immitis was cultured. The fate of this lesion was not mentioned, but the patient was alive and well several years later. In addition, Smith[1] cites a report of another patient with cavitation who died of coccidioidal meningitis. In general, there are few exceptions to the benign nature of the large number of asymptomatic pulmonary residuals. Unfortunately, not enough cases have been observed for a sufficient period of time to delineate the ultimate course of these chronic pulmonary residuals.

Therapeutic consideration is based on the factors of symptomatology, contagiousness, and incomplete knowledge of possible complications. It has been pointed out that most patients with chronic benign pulmonary residuals of coccidioidomycosis are asymptomatic and remain so for years in spite of persistent x-ray pathology. The noncavitary lesions usually remain stationary or regress, and the nodular type may even calcify. If a definite diagnosis can be established in these cases, no therapy is thought necessary.

However, when a cavity is present there is no uniform opinion as to its treatment. In 1953 Dr. D. T. Smith[10] stated that if coccidioidal cavities "do not heal in three to six months, they should be resected," and there is currently a growing interest in surgical therapy. The indications for surgery as expressed in the recent literature vary considerably. Forsee and Perkins[11] consider extirpative surgery to be the treatment of choice, even in the absence of distressing symptoms. Cotton[12] listed giant, blocked, secondary infected, or ruptured cavity, and hemoptysis, as surgical indications. To date there has been no controlled study to assess the relative risks and prognosis with surgical versus conservative therapy, and each case must be evaluated in the light of current knowledge. The risk of dissemination is slight; indeed, the presence of a cavity can be regarded as indicative of a high level of resistance on the part of the host. Contagion is apparently negligible.† There are no cases of man-to-man transmission of coccidioidomycosis reported in the literature, although experimental animals can be infected by installation of spherule-laden sputum into the bronchi,[15] and the mycelial forms which grow out on culture are highly infective for man. Therefore, we believe that the only rational basis for surgical therapy is the presence of symptoms or complications. Persistent or severe hemoptysis is an indication for surgical resection. A subpleural cavity may rupture and produce hydrothorax or induce

† References 13 and 14.

a bronchopleural fistula with hydropneumothorax or empyema, making surgical intervention necessary. Decortication may be necessary after a large organizing effusion. Collapse therapy, such as pneumothorax, pneumoperitoneum, or phrenic crush, is rarely indicated and is singularly unsuccessful in permanently collapsing a cavity.

In the absence of symptoms or complications the surgical risk must be weighed against the possibility of future complications. Surgery was performed in 14 cases in this series. Nine nodular lesions were excised for diagnostic purposes, without complications. Two of these were found to be blocked cavities on pathological examination. Hemoptysis, significant change in the lesions, or inability to make a definite diagnosis prompted surgical therapy in five cavity cases. Significant morbidity occurred in two of these cases. One patient developed loculated hydropneumothorax but recovered without further therapy. Another patient developed acute coccidioidal pneumonia, bronchopleural fistula, and empyema one month postoperatively, necessitating open drainage. Forsee and Perkins[11] report the occurrence of postoperative pulmonary spread of disease, bronchopleural fistula, empyema, or recurrent cavitation in 5 of 50 cases of resection of pulmonary residuals, 30 of which were cavitary cases. Cotton[2] reported a single postoperative death and 1 case of recurrent coccidioidal cavity in a series of 100 surgically treated cases. Recurrent cavitation has been reported by others.‡ Hence excisional therapy is not always curative. The possibility of dissemination following surgical resection is not a likely one. Snapper and co-workers[17] reported a case in which dissemination with coccidioidal meningitis apparently developed after resection of a nodular lesion (Case 1 in their paper), although there is insufficient information given to rule out preoperative disseminated disease. To our knowledge no other similar catastrophies are reported. Since dissemination will generally occur within six months after acute disease and is frequently accompanied by a high complement-fixation titer, excisional therapy should never be considered within this time interval or without knowledge of the serological titer.

‡ References 15 and 16.

The most frequent problem encountered in handling these lesions arises from the difficulty in distinguishing them from tuberculosis or tumor. A number of our patients were initially admitted to a tuberculosis service, and three patients received antituberculosis chemotherapy for varying lengths of time before the true diagnosis was established. With increasing awareness of the nature of coccidiodal residuals, this error should be infrequent. When tuberculosis or tumor cannot be excluded, excision of the lesion is necessary to determine the cause of the pathology. In our experience this has been the most frequent indication for surgery. A rare possibility for error, which must always be kept in mind, is the coexistence of tuberculosis or tumor and coccidioidal disease. Lastly, one may fail to differentiate between chronic residuals of a benign nature and disseminated coccidioidomycosis, of which pulmonary disease may be a feature. The disseminated form is distinguished by the presence of constitutional symptoms, elevated erythrocyte sedimentation rate, often high complement-fixation titers, occasionally negative coccidioidin skin sensitivity, and the finding of extrapulmonary granulomatous lesions.

Summary and Conclusions

The chronic benign pulmonary residuals of coccidioidomycosis are described, and the diagnosis and therapy of these lesions are discussed. This type of lung pathology may be frequently confused with tuberculosis neoplasm, or other pulmonary disease. Owing to the benign nature of coccidioidal residuals, no active therapy is usually required. Surgical therapy is necessary in cases with severe or persistent hemoptysis and large organized pleural effusions, and it may be advisable in cases of large, blocked, or expanding cavity.

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Clinical Diseases of Adults Associated with Sporadic Infections by APC Viruses

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The adenoidal-pharyngeal-conjunctival (APC) viruses are a large group of infectious agents comprising at present at least nine human and two simian types.[1] The first of these agents was discovered by Rowe,[2] who isolated it in cultures of adenoidal and tonsillar tissue removed at surgery. Types 1, 2, 5, and 6 appear to be common latent agents in such lymphoid tissue, but they have only rarely been implicated in spontaneous disease.* Type 3 APC virus was established as the etiologic agent in epidemic outbreaks of "pharyngoconjunctival fever," particularly in children, by Bell.[4] Type 4 appears to be identical with the RI 67 virus originally isolated and described by Hilleman and Werner[5] from cases of undifferentiated acute respiratory disease (ARD) or primary atypical pneumonia (PAP) in military recruits. Serological evidence implicated this agent as the important cause of epidemic respiratory illnesses, including ARD, in unseasoned troops in 1945[6] and since 1952.[7] Berge[8] recovered Types 3, 4, and 7 from military recruits suffering from respiratory illnesses ranging in severity from mild febrile rhinitis to primary atypical pneumonia at Fort Ord, Calif. Types 3 and 4 also produce eye infections with prominent follicular conjunctivitis.[9] Types 1, 2, 3, and 5 have been isolated on a few occasions from sporadic cases of nonbacterial pharyngitis in children.† Type 8 has been recovered from a case of epidemic keratoconjunctivitis and may be etiologically related to the disease.‡

The APC viruses appear to share a number of biological characteristics. They grow only in tissue cultures of certain human and monkey cells but do not infect laboratory animals or embryonated eggs. They are ether-resistant. All share a common complement-fixing antigen which appears to be of small particulate size and is sometimes called a "soluble" antigen. A serological reaction with this complement-fixing antigen can be found in the serum of persons infected with any type of APC virus. Thus the complement-fixation test gives only a broad indication of infection with the group of viruses but does not indicate the type involved. Immunity, on the other hand, appears to be strictly type-specific. For the typing of isolated viruses and for the measurement of type-specific antibodies, neutralization tests in tissue culture must be performed.

It is known from serological studies on various age groups in the civilian population that infection with APC viruses is common and that most adults have experienced infection with at least one and commonly two or three types.[3] In epidemic outbreaks of respiratory disease or conjunctivitis the symptoms and signs of the clinical illness are often well defined. However, it is unknown whether the majority of persons

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† Huebner, R. J.: Personal communication to the authors.

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undergo infection during epidemic spread of the virus, or whether its endemic presence results in sporadic infections leading to type-specific immunity.

During the past year we have had the opportunity of making the specific etiologic diagnosis of APC virus infection in a number of instances and of studying the clinical picture in considerable detail. These were sporadic cases in adults caused by Types 2, 3, 6, 7, or 8. The variety of clinical pictures presented by these cases was striking. It is the purpose of this paper to present reports which illustrate representative disease entities observed in the course of the study. Since infection with APC viruses, particularly of Type 4 (RI 67), has been prominently associated with respiratory diseases,§ we wish to call particular attention to the role of the eye, both as a site of primary or principal symptoms and as a possible portal of entry for the infection. Others have placed great emphasis on the role of APC virus infections in epidemics of military recruits and children. We wish to point out their role in sporadic infections of adults.

Methods and Materials

Patients.—The two main sources of clinical material were the eye clinic and the Student Health Service of the University of California Medical Center of San Francisco. Many physicians referred patients for study to the eye clinic, and Dr. Kahn Uyeyama called our attention to, and permitted detailed study of, patients under the care of the Student Health Service. Outpatients and inpatients were examined and treated by the service responsible for their care, but we saw, in consultation, every case described here. In addition to the usual laboratory examinations mandatory for the type of illness, special studies on each of these patients were directed toward establishing the viral etiology of the disease.

Virus Isolations.—Washings or scrapings from conjunctiva or cornea were obtained whenever the eye presented signs of involvement. Throat swabs were obtained from patients exhibiting respiratory symptoms. The specimens were suspended in maintenance medium (10% chick serum in Mixture 199), with the addition of antibiotics to prevent bacterial growth, and were either inoculated into tissue culture immediately or kept frozen at —20 C until used. HeLa cell tissue cultures in tubes were obtained from Tuskegee Institute, Ala. They were washed twice with Hanks' solution, and then 0.2 ml. of the specimen and 0.8 ml. of maintenance medium was added.‖ The tubes were incubated in a stationary position at 36 C for as long as the integrity of the HeLa cells permitted, usually 12 to 21 days, with occasional changes of maintenance medium when required by acid pH. The tubes were observed regularly at intervals of one or two days for cytopathogenic effects indicative of virus proliferation. When no evidence of virus activity was detected in the first tissue culture passage, at least one blind passage was made before the specimen was discarded as negative.

Viruses isolated in tissue culture were typed with known specific antisera through the assistance of Lieut. Col. T. O. Berge, 6th Army Area Medical Laboratory, and Dr. R. J. Huebner, National Institutes of Health.

Serological Tests.—Complement-fixation tests were performed in a conventional manner, using 2 full units of complement, 2 units of hemolysin, 2 units of antigen, and a 2% suspension of sheep cells. Sera were inactivated at 60 C for 20 minutes. The test was incubated overnight at 4 C and for 10 minutes at 37 C before the addition of sensitized cells. Readings were taken 10 minutes after the controls cleared completely. The antigen consisted of fluid from tissue cultures in which Type 3, 4, 6, or 8 APC virus had been grown. Immediately before use this fluid was heated at 56 C for 30 minutes, then centrifuged at 1000 rpm for 10 minutes.

For neutralization tests about 100 $T.C._{50}$ doses of infective virus were mixed with twofold serum dilutions and incubated at room temperature for one hour. Then 0.2 ml. of the mixture was inoculated into each tube of twice-washed HeLa cell cultures, and 0.8 ml. of maintenance medium was added. The tubes were incubated at 36 C in a stationary position and read daily in the conventional manner, denoting cytopathogenic effects by 1+ to 4+. Agreement between duplicate tubes containing the same mixture was good. The result was considered to show neutralization when there was a difference of 3+ in readings of experimental and control tubes for at least two consecutive days. Virus titrations and positive and negative control sera were included in each test.

Clinical Observations

Case 1 (Fig. 1).—A 26-year-old physician had suffered for three or four days from symptoms of an upper respiratory infection with pharyngitis,

§ References 5-8.

‖ All tissue culture media were obtained from Microbiological Associates, Bethesda, Md.

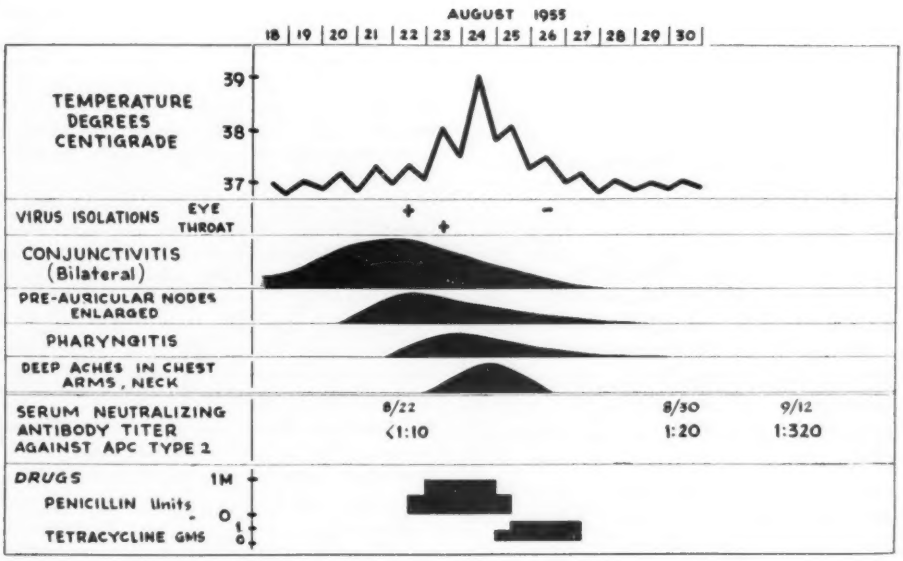

Fig. 1 (Case 1).—Course of acute infection with APC virus Type 2.

"congested nose," and enlarged cervical lymph nodes, when he suddenly developed conjunctivitis in the right eye, on Aug. 18. There was lacrimation and a burning sensation in the acutely inflamed eye. On Aug. 20 the right preauricular lymph node became markedly enlarged and slightly tender. The next day conjunctivitis developed in the left eye and the patient felt feverish.

When he was examined, on Aug. 22, the patient's temperature was 37.4 C orally. Both eyes had 20/20 vision and normal corneal sensitivity. The cornea was clear, and there was no flare, precipitates, or cells in the anterior chamber. The lids were normal. There was marked tearing and congestion of the conjunctivae of both eyes (right more than left), with intense follicular hypertrophy, particularly in the lower fornix. There was a tender 1×2 cm. right preauricular lymph node. The throat was injected and edematous, with a small amount of exudate on the posterior pharyngeal wall. Cervical lymph nodes of the right anterior chain were enlarged and tender. The remainder of the physical examination was not remarkable.

On Aug. 23 the patient felt more severely ill and was admitted to the hospital. His temperature was 101.8 F; pulse rate, 108, and blood pressure, 150/70. He complained of a severe headache and an extremely sore throat. He was prostrated with persistent deep aches in shoulders, neck, and arms, described as "influenzal." The appearance of the throat and the right eye was unchanged from the previous day, but the left eye was clear. The preauricular and cervical nodes persisted enlarged and tender. There was a slight cough and some aching in the chest, but the lungs were clear to examination. The remainder of the physical examination was not remarkable.

Laboratory examination revealed the following: Hgb., 16.8 gm. per 100 cc.; packed cell volume (PCV), 48%; WBC, 8950 per cu. mm. (polymorphonuclear cells, 79%; lymphocytes, 12%; monocytes, 9%); corrected erythrocyte sedimentation rate, 10 mm. in an hour; urine, negative; heterophile agglutination test, 2+ in dilution 1:28.

Course.—The prostration, deep "influenzal" aches, intense conjunctivitis of right eye, and very sore throat persisted through Aug. 25 and then gradually subsided. The conjunctivitis had largely subsided on Aug. 27. The pharyngitis was last to disappear, but on Aug. 29 the patient was entirely well and was discharged home.

Observations on Etiology.—A. Bacteriological Cultures: From lids and conjunctivae only a few nonhemolytic Staphylococcus albus organisms were grown. A throat culture showed only the normal bacterial flora.

B. Cytology: Smears from the lids showed numerous polymorphonuclear leucocytes. Smears from the conjunctivae contained only a small number of mononuclear cells and occasional polymorphonuclears.

C. Virus Isolations: Washings were obtained from the right eye on Aug. 22 and 26 and from the left eye on Aug. 25. Throat swabs were secured on Aug. 23. All materials were inoculated into twice-washed HeLa cell cultures immediately or after storage at —20 C for 3 to 60 days.

The washing of the right eye (Aug. 22) and the throat swab (Aug. 23) both yielded APC viruses shown to belong to Type 2.

D. Neutralization tests performed with the patient's serum against the virus isolated from him indicated a definite rise in antibody titer.

Date Serum Obtained	Neutralization Titer
Aug. 22	1:10
Aug. 31	1:20
Sept. 12	1:320

Comment.—When this patient was first seen in the clinic he had pharyngitis, conjunctivitis, and low-grade fever—highly suggestive of "pharyngoconjunctival fever,"[4] generally a mild, brief illness. Subsequently, however, he became severely ill and presented the picture of severe influenza—except for his very abrupt recovery, without protracted convalescence. The isolation of Type 2 APC virus from both eye and throat and the marked rise in specific neutralizing antibody to this type established it as the etiologic agent.

While Type 2 APC virus has been isolated repeatedly from adenoids of children, there is only one published reference to this type being recovered from an illness.[12] Apparently the agent can be carried latently in the tissues of children and yet can produce a disease of considerable severity when infecting a susceptible adult. The source of infection for our patient remains entirely unknown. As a physician, he had had contact with a large number of persons, both sick and well. However, he recalled no recent contact with children, or with adults suffering from the type of illness he developed. The portal of entry likewise is uncertain. The patient suffered from symptoms of upper respiratory infection before the conjunctivitis appeared. However, he was subject to frequently recurrent sinusitis with postnasal drip, a condition which could mimic his early respiratory symptoms. Thus perhaps the conjunctivitis represented his earliest specific symptom of APC infection.

Case 2.—A 31-year-old male resident physician noted a foreign body sensation and burning in his left eye on Oct. 25, 1955. Twelve hours later he observed an acute conjunctivitis and slightly enlarged tender left preauricular node. There was no respiratory tract involvement whatsoever. Examination on Oct. 25, 1955, revealed an acute follicular hypertrophy, marked injection of the left conjunctiva, and a barely palpable left preauricular node. The remainder of the physical examination was not contributory. The temperature was normal.

The conjunctivitis of the left eye subsided gradually in five days. However, on Nov. 4 the right conjunctiva became intensely injected, with some lacrimation. This condition subsided uneventfully in two days.

Observations on Etiology.—A. Bacteriological Cultures: From the conjunctiva no growth was obtained. From the lids a few colonies of S. albus and a diphtheroid were grown.

B. Cytology: The exudate contained many mononuclear cells, a few polymorphonuclears, some keratinized epithelial cells, but no eosinophiles.

C. Virus Isolation: A washing from the left conjunctiva was obtained on Oct. 25. It yielded an APC virus in tissue culture later identified as Type 3. No virus could be isolated from throat swabs obtained on Oct. 26.

D. Serological tests performed with the patient's serum gave the following results:

	Date Serum Obtained	
	Oct. 25	Dec. 7
Complement-fixation test with APC antigen	<1:10	1:40
Neutralization titer against APC virus Type 3	<1:10	1:40
Neutralization titer against APC virus Type 8	<1:10	<1:10

Case 3.—A 41-year-old business man developed an acute conjunctivitis of the right eye on Aug. 13, 1955. He also had a sore throat, but there was no rhinitis. Examination on Aug. 16 showed a temperature of 99.2 F, normal-appearing pharynx, and a papillary and follicular conjunctivitis of the right eye with enlarged right preauricular lymph node. The submaxillary nodes were enlarged bilaterally. On Aug. 19 the left eye became involved with the same type of reaction, but then the patient suddenly improved, and on Aug. 23 he was entirely well.

Observations on Etiology.—A. Bacteriological Cultures: Only rare colonies of nonhemolytic S. albus grew from a conjunctival specimen.

B. Cytology of Conjunctival Exudate: A few mononuclear and polymorphonuclear cells; no eosinophiles.

C. Virus Isolations: A washing and a scraping from the right conjunctiva, obtained on Aug. 16, both yielded an APC virus identified as Type 3.

D. Serological tests performed with the patient's serum gave the following results:

	Date Serum Obtained	
	Aug. 16	Sept. 2
Neutralization titer against APC virus Type 3	<1:10	1:80
Neutralization titer against APC virus Type 6	<1:10	<1:10
Complement-fixation test with APC antigen	<1:10	<1:40

Comment.—The previous two cases are representative of six with APC virus Type 3 infection in whom we were able to establish the etiology. One case of Type 6 infection reported elsewhere[13] was very similar in most respects. These adults had consulted their physicians principally for an acute follicular conjunctivitis. The eye was painful and red, and the corresponding preauricular lymph node was enlarged. Systemic or respiratory involvement was mild or absent, and usually there was no fever. These cases could readily be mistaken for simple bacterial conjunctivitis were it not for negative bacteriological cultures, virus isolations, and the antibody titer rise suggesting systemic involvement. Such clinical pictures are perhaps the adult equivalent of "pharyngoconjunctival fever" seen in children. In these seven patients viruses were isolated from the eye only, not from the throat. The conjunctivitis usually involved only one eye at first, but the second eye became involved three to nine days later and virus could be isolated from it. The involvement of the second eye usually was milder and of shorter duration.

We attempted recovery of APC viruses from the eye in 22 patients whose clinical picture strongly suggested this etiology and who were seen within one week of onset of symptoms. From 11 of these patients viruses were isolated. Two of these viruses were herpes simplex (without corresponding rise in specific antibody titer in the patient): the remaining nine were APC viruses of Types 2, 3, 6, and 8. Thus it appears that specimens from the conjunctiva and cornea, when there is manifest involvement of these structures, yield APC viruses readily, even in sporadic cases not seen very early in the disease.

CASE 4.¶—A 29-year-old white married student was admitted to the hospital on Oct. 18, 1955, with the chief complaint of malaise, fever, and cough for four days. He had felt quite well until Oct. 14, when he noted slight headache and malaise. The next day the headache was severer. The throat was sore, and he noted some joint pains. Next there developed fever up to 38.2 C, a feeling of constriction in the chest, and a cough productive of only a little white phlegm.

On admission the patient appeared moderately ill, with a temperature of 102.2 F; pulse rate, 104; respirations, 28. The skin was flushed. The conjunctivae were injected, and there was photophobia. There was injection of the posterior pharyngeal wall, covered by a nonpurulent glassy exudate. A few nontender anterior cervical lymph nodes were palpated. Physical examination of heart, lungs, and abdomen was noncontributory, and the reflexes were normal.

Laboratory findings on Oct. 18 showed a hemoglobin of 16.1 gm. per 100 cc.; PCV. 45%; corrected erythrocyte sedimentation rate, 23 mm. in an hour. The white blood cell count 10,550, with a normal differential count (polymorphonuclear cells, 75%; lymphocytes, 16%; monocytes, 6%). The urine was normal. A bacteriological culture from the throat showed only the normal flora. A tuberculin test (O.T. 1:1000) and a coccidioidin test (1:100) were both positive. X-ray examination

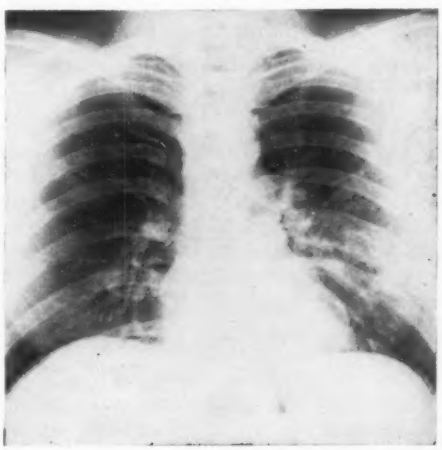

Fig. 2 (Case 4).—Chest film, Oct. 18, 1955, showing consolidation of left midlung field.

¶ Dr. Kahn Uyeyama gave permission to report this case and made available to us specimens for diagnostic study.

of the chest indicated a pneumonitis of the left lung, involving predominantly the lingula of the left upper lobe (Fig. 2).

Course.—On Oct. 18 the patient received intramuscular penicillin, and from Oct. 19 to 25 he was given oral tetracycline. The antibiotics had no noticeable effect on his illness. His temperature was 100.4 F or higher on three days; it then subsided. During his hospital stay the patient did not raise any sputum, and his cough subsided about Oct. 24. Crackling rales were heard over the left lung field and in the left axilla from Oct. 20 to 26. X-ray examination of the chest on Oct. 26 showed very marked resolution of the pneumonic process (Fig. 3). The patient improved rapidly

Fig. 3 (Case 4).—Chest film, Oct. 26, 1955, showing virtually complete return to normal of left lung field.

and was discharged, feeling well, on Oct. 27. Cold agglutination tests performed with serum drawn on Oct. 17 and 31 were negative in a dilution of 1:5.

Virological Studies.—A throat swab obtained on Oct. 17 was inoculated into HeLa cell cultures, but no virus was recovered. Serological studies performed on acute and convalescent sera gave the following results:

	Date Serum Obtained	
	Oct. 17	Oct. 31
Neutralization titer against APC virus Type 3	<1:10	<1:10
Neutralization titer against APC virus Type 4	<1: 8	<1:16
Neutralization titer against APC virus Type 7	1:16	>1:64
Complement-fixation test with APC antigen	<1:10	>1:80

Serological tests for Q-rever and psittacosis were negative.

Comment.—The clinical diagnosis in this case was primary atypical pneumonia. Clearly the patient had a nonbacterial pneumonitis without cold agglutinins and associated with a very marked rise in complement-fixing antibodies to APC virus antigen. He thus resembled the cases observed by Hilleman[7] in military populations during 1952-1954 and by Berge[8] during 1953-1954. In these studies APC viruses, Types 3, 4, and 7, were associated with the clinical picture of primary atypical pneumonia. While no virus was isolated from our case, the results of the neutralization tests definitely implicate Type 7 as the etiologic agent.

Infection with certain APC viruses must be accepted as one possible cause of nonbacterial pneumonitis, clinically indistinguishable from primary atypical pneumonia, but without cold agglutinin formation, and not responding to antibiotics. The source of the infectious agent was of considerable interest in this case. Since this patient was a student on a small university campus, 10 other students who developed respiratory illnesses at the same time were investigated for serological evidence of APC virus infection. Acute and convalescent sera were compared by complement-fixation test against APC virus antigen. Of the 10 patients, 2 had no demonstrable antibodies; in 3 the titer was 1:20; in 1, 1:40, and in 3, 1:80. None of these persons showed a rise in antibody titer between the first and the second serum specimen. Thus it can be tentatively concluded that APC viruses represented by the antigen used in the complement-fixation test were not responsible for, or associated with, the respiratory illness. Furthermore, these tests did not suggest prevalence of Type 7 or any other APC virus in the campus population during the illness of Patient 4. His home contacts could not be investigated.

Case 5.—A 50-year-old merchant seaman who traveled between the Orient and San Francisco was seen in the eye clinic on the 12th day after

onset of an intense bilateral conjunctivitis with pseudomembrane formation and tender greatly enlarged preauricular lymph nodes. There was also keratitis which, in the course of the next few days, led to the development of round subepithelial opacities highly characteristic of epidemic keratoconjunctivitis. These opacities have persisted for at least seven months. The patient had no fever, respiratory, or systemic symptoms at any time. His nurse acquired the typical disease on the 10th day of exposure to this patient.

Observations on Etiology.—A. Bacteriological Cultures: A few S. albus organisms were grown from the conjunctiva on the right; no bacteria were obtained from the left eye.

B. Cytology: Smears from the conjunctivae showed a predominance of polymorphonuclear cells.

C. Virus Isolation: Scrapings from conjunctivae were inoculated into HeLa cell cultures. The first cytopathogenic effects occurred on the 17th day of incubation, and degeneration was complete on the 22nd day. The virus was not neutralized by antiserum to any of the then-known types of APC virus (1 to 7), but, because it obviously resembled other APC viruses in biological properties, Dr. R. J. Huebner, at the National Institutes of Health, proposed that it be designated Type 8.

D. Serological Tests: Neutralization tests performed with the patient's serum against the virus isolated from him gave the following results:

Neutralizing antibody titer against APC virus Type 8	Days After Onset, No.		
	12	99	141
	? (Toxic serum)	1:40	1:160

Comment.—The virus isolated from this patient forms the prototype of APC virus Type 8. It differs in a number of biological characteristics from the other agents in the group, particularly in its low infectivity for HeLa cells and its severe involvement of the cornea. A serological survey, including sera from the U. S., Japan, and Italy, indicates a very striking association between infection with this virus and epidemic keratoconjunctivitis, as summarized below. The etiologic relationship of this virus to the disease, however, remains to be clarified. It should be noted that systemic illness, respiratory symptoms, or fever are rarely present in epidemic keratoconjunctivitis.

	Patients, No.	Neutralizing Antibodies to APC Type 8	
		<1:10	>1:10
Epidemic keratoconjunctivitis	70	4 (5.7%)	66 (94.3%)
Controls (other eye diseases, normals, miscellaneous infections)	118	109 (92.4%)	9 (7.6%)

Comment

The advent of new simple methods for the isolation of viruses in tissue culture augurs well for the discovery of a vast number of "new" viruses from many different areas of the human body. The problem will be not to find viruses but to decide which of them form a "normal viral flora" corresponding to the well-established normal bacterial flora which is not primarily associated with disease. Increasing numbers of viral agents are being discovered which are "in search of disease" and therefore called "orphan" viruses.

When the first APC viruses were discovered in cultures prepared from adenoidal and tonsillar tissues it seemed probable that they, too, might be predominantly "orphans." The subsequent identification of Type 3 as the etiological agent causing epidemic pharyngoconjunctival fever in children [4] and the discovery that the RI 67 virus (APC Type 4) caused large outbreaks of respiratory disease in military recruits # indicated that at least some APC viruses were pathogens of considerable stature. The present report attempts to show that this might be true for many of the known APC virus types, including some—like Types 2 and 6—which have not often been isolated from disease. It also indicates that sporadic infections of adults are by no means rare.

The question arises whether specific symptom complexes or clinical entities might be associated with infection by specific types of APC agents. Because of the paucity of clinical observations, an answer

References 5-7.

is evidently not possible at this time. If Type 8 is not only associated with, but etiologically involved in, epidemic keratoconjunctivitis, then it is indeed responsible for a well-defined entity. For the other types, it can only be said at this time that a significant degree of association between type and clinical illness appears possible: e.g., Types 4 and 7 with respiratory disease, including nonbacterial pneumonitis; Type 3 with isolated conjunctivitis. On the other hand, it is becoming clear that a wide range of illness, from minimal to severe and involving one organ system or many, can be encountered with a number of different types, including Types 2, 3, 4, and 7.

The majority of proved sporadic APC virus infections in adults which we have observed have shown involvement of the eye. In some the eye was the only site of manifest viral activity; in others it was associated with systemic or respiratory symptoms. The constancy of eye involvement raises the question whether the eye may not serve as portal of entry for the virus. This thought is suggested by the great difficulty of infecting volunteers with APC viruses via the respiratory tract * and the relative ease of obtaining infection when virus is applied to the conjunctiva.[14] Furthermore, we have observed instances [13] in which the conjunctivitis was the first symptom noted and definitely preceded systemic symptoms by several days. It is quite possible that in civilian practice APC virus infections of adults may manifest themselves frequently as eye infections and only rarely as respiratory diseases.

Summary

Adenoidal-pharyngeal-conjunctival (APC) viruses are widely accepted at present as important etiological agents of epidemic respiratory disease in military recruits or in children. This paper attempts to throw light on their role in the etiology of sporadic illness in adults. Five case reports are presented illustrating infection with APC viruses of Types 2, 3, 6, 7, and 8. The illnesses ranged from simple monocular conjunctivitis without fever or respiratory symptoms to a severe influenza-like systemic disease necessitating prolonged hospitalization. The role of the eye as a probable portal of entry and a site of major manifestations of APC virus infection is emphasized.

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Factors Associated with Changing Sex Ratio of Myocardial Infarction

Study with Special Reference to the Disproportionate Rise in Incidence of the Disease Among Older Women

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In a recent epdemiological study of autopsied patients with acute myocardial infarction, at Washington University, it was discovered that a shift has occurred in recent years in the relative incidence of the disease in the two sexes.[1] In the period 1910-1939 the incidence of acute myocardial infarction was twice as great in men as it was in women. In the period 1940-1954 the incidence was not significantly greater in men than in women. The results in a portion of the latter period have been confirmed by Acher, Burchell, and Edwards,* who found a similar ratio (1:1) between the sexes among the patients with acute myocardial infarction autopsied at Mayo Clinic during the period 1946-1950. Such a shift is of profound significance and warrants a careful search for factors that may be responsible. The purpose of this report is to present the results of a study of various factors associated with the changing ratio between the sexes with acute myocardial infarction in the Barnes Hospital series.

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*Achor, R. W. P.; Burchell, H. B., and Edwards, J. E.: Personal communication to the authors.

Material and Methods

Data were obtained from the autopsy and clinical records of Barnes Hospital and the Department of Pathology of Washington University for the period 1910-1954. During this period 8183 autopsies were performed on adults (over 20 years of age) from Barnes Hospital, and among these were 500 with acute myocardial infarction. These patients have been characterized as a complete group in several ways in previous publications.† In the present study they have been divided into two groups: (1) those who died prior to 1940 and (2) those who died between 1940 and 1954, and each group has been characterized separately and compared with the other. Data obtained for comparison include age, sex, body weight, weight of kidneys, and history of diabetes mellitus.

Results

The results are presented in the Table and in the Figure.

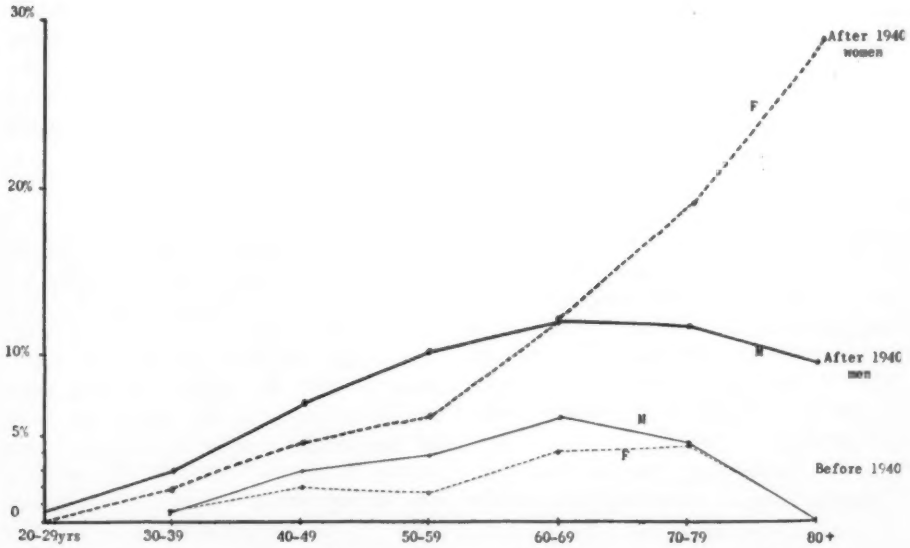
Between 1910 and 1939 there were 83 autopsied patients with acute myocardial infarction among the 3368 autopsies from Barnes Hospital, and of these 83 cases, 63 were men (representing 3% of all autopsies performed on adult men during the same period) and 20 were women (representing 1.56% of all autopsies on adult women during the same period). During the years 1940 through 1954 there were 417 patients who died with acute myocardial infarction among the 4815 autopsied adults from Barnes Hospital, and of these 417 cases 217 were men (9% of all autopsies on adult men during this period) and 146 were women (8% of all autopsies on adult women during this period). The average ages of men with acute myocardial in-

† References 1 and 2.

Comparison of Various Factors Among Autopsied Patients with Acute Myocardial Infarction from Barnes Hospital Between Two Periods (1910-1939 and 1940-1954)

	1910-1939	1940-1954
Average age, Yr.		
Male	58	61
Female	57	65
Average body weight, kg.		
Male	66	70
Female	64	61
Percentage of patients whose weights exceed ideal weight by 10% or more		
Male	16.3	37.2
Female	52.9	45.8
Average weights of kidneys, gm.		
Male	343	357
Female	299	293
Incidence of diabetes mellitus, %		
Male	19	12
Female	30	32

farction between 1910 and 1939 and between 1940 and 1954 were 58 and 61 years, respectively, and the corresponding averages for women were 57 and 65 years. The average body weights of men in the two periods were 66 and 70 kg., respectively, and the corresponding body weights of women were 64 and 61 kg. According to the standard tables of ideal weights for heights prepared by the Metropolitan Life Insurance Company,‡ 16.3% of men in the period of 1910-1939 and 37.2% of men in the period of 1940-1954 who died with acute myocardial infarction weighed at least 10% more than the maximum figure of the ideal weight range for medium frame. The corresponding figures for women in the two periods were 52.9% and 45.8%, respectively. Average weights of kidneys for men in the two periods were 343 and 357 gm., respectively, and those for women were 299 and 293 gm. The incidence of diabetes mellitus among men with acute myocardial infarction was 19% in the period 1910-1939 and 12% in the period 1940-1954, and the corresponding figures for women were 30% and 32%.



Incidence of acute myocardial infarction among total adult male and female autopsies of the Barnes Hospital by age and period (before and after 1940). Percentage figures plotted in the figure are derived by dividing the total number of Barnes Hospital autopsies performed on patients of the age, sex, and period indicated into the total number of autopsied patients with acute myocardial infarction of the age, sex, and period indicated.

Comment

Age.—The most important observation made in this study is the sharp rise in recent years in the incidence of acute myocardial infarction among older women in the

‡ References 3 and 4.

Barnes Hospital autopsy series. The incidence actually increased in all age-groups in both men and women in the period 1940-1954 as compared with the period 1910-1939. However, the increase was uniform for all age-groups in men and for the younger age-groups of women. The sharp rise in incidence in older women is far greater than that of younger women or than that of men at any age.

This disproportionate increase in the incidence of acute myocardial infarction among older women accounts for most and perhaps all of shift in the ratio between the two sexes (2 men to 1 woman for the period 1910-1939 and 1:1 for the period 1940-1954).

Body Weight.—Changes in body weight are unlikely to account for the changing sex ratio. The average body weights of women were similar in the two periods (1910-1939 and 1940-1954), and the percentages of women whose weights exceeded the ideal weight range [5] were similar in the two periods.

The percentage of men whose weights exceeded the ideal weight range was greater in the period 1940-1954 than in the previous period. Hence, if body weights were a very important factor in the development of acute myocardial infarction in the series the ratio of incidence between the two sexes should have changed in the opposite direction instead of to 1:1.

Hypertension.—In a previous study [2] designed to evaluate the role of hypertension in coronary arteriosclerosis the combined weight of kidneys was used as an objective index to the degree of systemic hypertension during life. The same method was applied in the current study to evaluate the role of systemic hypertension in the changing sex ratio of the incidence of acute myocardial infarction. There was no significant difference in the average weights of kidneys in either sex in the two periods, suggesting that hypertension did not play an important role.

Diabetes Mellitus.—Diabetes mellitus was four times as common among patients with acute myocardial infarction as among our adult general autopsy population,[1] indicating that diabetes mellitus was an important factor in the development of acute myocardial infarction. Diabetes mellitus was commoner among women with acute myocardial infarction than among men: Hence, the sex ratios of the incidence of acute myocardial infarction are different among diabetics (0.8 man to 1 woman) than among nondiabetics (1.5 men to 1 woman). However, the incidence of diabetes mellitus among women with acute myocardial infarction was not significantly greater in the period 1940-1954 than in the previous period. Hence, diabetes mellitus cannot account for the disproportionate rise in incidence of acute myocardial infarction among women in the more recent period. The comparison of diabetics and nondiabetics will be developed further in a subsequent report.

Summary

In a previous epidemiological study of autopsied patients with acute myocardial infarction at Barnes Hospital, we found a shift in the ratio of incidence of acute myocardial infarction in the two sexes. Prior to 1940 the incidence of acute myocardial infarction in this series was twice as high among men as among women, and during the period 1940-1954 the incidence was as high among women as it was among men. In the current study various factors which may account for the changing ratio between the sexes with acute myocardial infarction are analyzed and discussed.

The most remarkable observation made is that the shift in the ratio of the incidence of acute myocardial infarction between the two sexes is due to a disproportionately sharp increase in the incidence of acute myocardial infarction among women over 60 years of age during the period of 1940-1954.

Among women, neither the average body weight nor the percentage whose weights exceeded the ideal weight range was significantly different in the two periods. Thus it seems unlikely that changes in body weight account for the disproportionate rise in incidence among women.

When the weight of kidneys is used as a rough guide to the incidence and severity of systemic hypertension during life and a comparison is made between the average weights of kidneys in the two periods, no significant differences are found in either sex.

Diabetes mellitus cannot account for the sharp increase in the incidence of acute myocardial infarction among women, since the incidence of diabetes mellitus among women with acute myocardial infarction is similar in the two periods.

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The Characteristics of Nonfatal Myocardial Infarction in the Aged

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Introduction

The Home for Aged and Infirm Hebrews is an institution with a census of more than 900 persons over the age of 60. In the course of the long-term medical management of this population it became apparent that the characteristics of nonfatal myocardial infarction in this group departed from the clinical picture commonly associated with this disease. It was felt that an analysis of the incidence and clinical features of nonfatal myocardial infarction would be helpful in the diagnosis and treatment of cases in this age group.

Material and Methods

The records of 700 ambulatory residents of the Home were reviewed for evidence of myocardial infarction over the five-year period from 1951 through 1955. In addition to data from intercurrent illnesses, the results of routine annual complete examinations, including history, physical examination, electrocardiogram, complete blood cell count, urinalysis, chest x-ray, blood sugar, and urea nitrogen, were available. Illness of this type is taken care of completely within the institution; full clinic and hospital records are maintained, and there is sufficient stability of medical and nursing staff to insure a high degree of reliability and completeness of knowledge about the complaints and physical and mental state of any given resident.

In all cases in which presumptive evidence of myocardial infarction was present on the electrocardiograms, a careful study was made for evidence of change in the white blood cell count, sedimentation rate, temperature curve, and blood pressure and signs of the onset of congestive heart failure. Note was made of any relevant symptomatology, such as precordial or substernal pain, pressure, constriction, numbness, etc.; similar sensations in the neck, upper extremities, or abdomen; dyspnea; orthopnea; shock; cough; dizziness; vertigo; nausea, or vomiting. Special note was made of the mental status preceding or following the infarction, with emphasis on memory defect, general reactivity and self-expression, disorientation, and depression.

Only cases with major degrees of mental impairment were noted, as in this age group lesser degrees of impairment, particularly of memory, are sufficiently common to call for no special clinical comment.

Electrocardiographic Criteria for the Presumptive Diagnosis of Myocardial Infarction

The earlier records included Leads I, II, 3, aV_R, aV_L, aV_F, V_2, V_4, and V_5. The later records included Leads V_1, V_3, and V_6 in addition. The electrocardiographic changes considered as presumptive of myocardial infarction were those commonly accepted in the literature and well outlined by Wilson,[1] Barker,[2] and Goldberger.[3]

A set of criteria was developed in order to rule out of the study cases in which electrocardiographic changes might have been due to other causes. The papers of Wilson,[1] Levine,[4] and Wasserman, Bellet, Saichek[5] were useful in this respect.

The development of ischemic T-wave changes of the cove plane type are the least specific evidence for myocardial infarction, since they may develop for a variety of other reasons. Cases with the gradual development of T-wave inversion over a long period of time were excluded, since in the aged prolonged low-grade coronary insufficiency or repeated minor episodes of coronary insufficiency on a substrate of preexistent and progressive coronary sclerosis with narrowing may cause subclinical diffuse foci of necrosis and subsequent fibrosis with T-wave inversion. T-wave inversions associated with the use of

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digitalis and quinidine and the use of vasopressor agents were excluded. T-wave inversions associated with hypokalemia and uremia were excluded. T-wave inversions associated with the development of left ventricular hypertrophy, pulmonary embolism, the post-tachycardia syndrome, bundle-branch block, the later stages of pericarditis, and episodes of acute coronary insufficiency were also excluded.

Characteristic reciprocal S-T segment elevations and depressions, particularly of a serial nature, are accepted as being more specific for infarction than changes in the T-waves. However, such conditions as pulmonary embolism, left ventricular hypertrophy, the post-tachycardia syndrome, acute pericarditis, bundle-branch block, hypokalemia, and digitalis therapy may be associated with S-T changes and were excluded. Also excluded were the S-T elevations which may occur in the right precordial leads of normal persons.

QRS changes such as the development of a broad deep Q-wave and loss of R-wave amplitude are accepted as being due to transmural infarction in almost all cases. We excluded cases where such changes could be attributed to pulmonary embolism, with a transiently deep Q Wave in Lead III. There were no cases with the deep Q in the right precordial leads associated with right ventricular hypertrophy.

We realize that occasional cases of severe coronary insufficiency occur with QRS, S-T, and T-wave changes indistinguishable from those of infarction, but these were excluded by their duration of only a few days; by the absence of fever, leucocytosis, and elevation of the sedimentation rate, and by the presence of such obvious precipitating factors as tachycardia, infection, surgical shock, overexertion, etc. The transient 5- to 30-minute T-inversions and S-T segment depressions associated with milder degrees of coronary insufficiency were more easily excluded by their short duration. The exclusion of the severer degrees of coronary insufficiency, while subject to some question on the basis of pathology, is justified by the difference in prognosis and treatment.

Cases with the development of bundle-branch block were excluded, except where characteristic deep Q-waves appeared in the right precordial leads in right bundle-branch block, or serial T and S-T changes were noted.

It is appreciated that in this type of study some cases of myocardial infarction may have been missed due to small size, unusual location, the use of only three precordial leads in some of the earlier records, and the return to normality or to a nondiagnostic pattern in the maximum one-year interval between records in the completely asymptomatic cases.

Results

Fifty-one patients were found who were considered to have had an acute nonfatal myocardial infarction during the five-year period studied. In 16 cases, no history was obtainable of any symptoms referable to heart disease, and these were considered as presumptive silent infarctions. In 21 cases anterior chest, neck, upper extremity, or epigastric pain or equivalent sensations such as oppression or constriction were absent, but other substitution symptoms such as dyspnea, syncope, dizziness, vertigo, cough, nausea, or middle or lower abdominal pain were predominant. These were considered as presumptive atypical infarctions. Fifteen cases with anterior chest, neck, upper extremity, or epigastric pain or equivalent sensations were considered to be typical cases.

The comparative clinical data are presented in Tables 1 and 2.

The 16 typical cases consisted predominantly of hypertensive men under age 71, without preceding severe mental deterioration and with normal hearts on x-ray and electrocardiogram. Their infarctions were accompanied by the expected changes in white blood cell count and sedimentation rate and by an elevation of temperature. Their electrocardiograms showed serial changes and a high incidence of significant Q-waves and reciprocal S-T segment

TABLE 1.—*Predominant Clinical Symptomatolgny with Presumptive Acute Myocardial Infarction*

	Cases, No.		
	Silent (16 Cases)	Atypical (21 Cases)	Typical (15 Cases)
No symptoms	16	0	0
Precordial and/or upper extremity pain	0	0	15
Dyspnea (with heart failure)	0	7	0
Dyspnea with pneumonia	0	3	0
Weakness and dizziness	0	4	0
Weakness (with heart failure)	0	1	0
Restlessness and confusion	0	1	0
Dizziness and nausea	0	2	0
Abdominal pain only	0	2	0
Abdominal pain (with heart failure)	0	1	0
Diagnosis of acute myocardial infarction prior to electrocardiographic interpretation	0	1	15

TABLE 2.—*Clinical Findings in Silent, Atypical and Typical Myocardial Infarction*

	Cases, No.		
	Silent (16 Cases: M, 9; F, 7)	Atypical (21 Cases: M, 9; F, 12)	Typical (15 Cases: M, 11; F, 4)
Age range, Yr.			
61-70	4	4	3
71-80	6	9	10
81-92	6	8	2
Preceding severe mental deterioration	1	5	2
Preceding hypertension (over 150/90)	10	15	1
Preceding normal or mildly abnormal electrocardiogram	14	9	13
Preceding enlarged heart on x-ray	4	9	2
Significant fall in blood pressure	1	2	9
Elevation of temperature, sedimentation rate, and leucocytosis	2	13	13
Serial electrocardiographic changes	3	16	15
Type of electrocardiographic changes			
Q-wave	5	3	7
S-T segment	4	5	8
T-wave	16	21	15

changes. The majority had a significant fall in blood pressure. The diagnosis on clinical grounds was made in all prior to electrocardiographic confirmation.

The 21 atypical cases consisted predominantly of hypertensive persons about evenly distributed between the 71 to 80 and 81 to 90 age ranges, with an appreciable number showing preceding severe mental deterioration and with a high incidence of enlarged hearts on x-ray and abnormal electrocardiograms. Their infarctions were accompanied by the expected changes in white blood cell count, sedimentation rate, and elevation in temperature in the great majority. The great majority had serial electrocardiographic changes but with a low incidence of development of significant Q-waves and reciprocal S-T segment changes. Only a few had a significant fall in blood pressure. Only in one was the diagnosis made on clinical grounds prior to the interpretation of the diagnostic electrocardiograms. The predominant symptoms were dyspnea, dizziness, weakness, low abdominal or midabdominal pain, nausea, and restlessness and confusion, in that order of frequency.

The 16 silent cases consisted predominantly of persons evenly distributed in the 71 to 80 and 81 to 90 age ranges, without preceding severe mental deterioration. About half were hypertensive, and the great majority had normal hearts on x-ray and normal electrocardiograms. Changes in sedimentation rate, white blood cell count, and temperature were found in only a few. Serial electrocardiographic changes were present in only a few, though about a third showed significant Q-waves and reciprocal S-T segment change. Only one had a significant fall in blood pressure. A clinical diagnosis was not made in any of this group on other than electrocardiographic grounds.

Comment

The comparative number of cases in the three groups reveals a predominance of presumptive nonfatal atypical and silent infarctions in a five-year survey of a large population of ambulatory aged. The small number of cases in each group makes comparison of the differences between them at best suggestive. However, rationalization of these differences may be helpful in the explanation of the high frequency of occurrence of such atypical and silent infarctions in the aged.

The appreciation of pain in the typical group may be explained on the basis of their being a younger group, with little mental deterioration, who would appreciate and verbalize such a sensation more clearly. In addition, their infarctions, being more severe

in nature, would be more likely to cause an acute sensation and evoke more detailed history taking. Obviously the presence of pain would aid in earlier diagnosis and more intensive clinical and laboratory observation, with an increase in the incidence of positive findings. The absence of the stimuli of preceding cardiac damage, i.e., coronary disease on electrocardiogram and hypertrophy on x-ray, might be correlated with a less-well-developed collateral circulation and more extensive infarction and pain, as shown by the greater incidence of major electrocardiographic changes and falls in blood pressure.

The explanation for the lack of pain and the presence of atypical symptoms in the atypical group lies in several factors. First, the high incidence of severe mental deterioration may well cause a loss of meaning (or emotional component) of pain sensation, as shown by Marchand [6] and Lieberman [7] in mental hospital patients with acute infarction, while symptoms attributable to decreased cardiac output are appreciated. Cookson [8] says that there is a reduction in arterial elasticity and degenerative vascular changes in the cerebral vessels with aging which sensitizes the cerebrum to reductions in blood flow. With acute infarction a vasomotor reflex results in increased vagal influence, causing bradycardia and abnormal rhythms. This causes a reduction in cerebral blood flow and symptoms such as syncope, dizziness, vertigo, etc. in the aged. Thus, a reduced cardiac output plus a sluggish carotid sinus reflex mechanism together with an impaired cerebral circulation causes partial cerebral anoxemia. Papp [9] notes, in studies of cerebral anoxemia, that pain sensation is lost early and returns late during recovery.

In this series, 8 of 21 atypical cases had symptoms referable to cerebral anoxemia, such as dizziness, weakness, and confusion, without pain. We had no cases with the most dramatic manifestation of this phenomenon, i.e., acute infarction with complete heart block and bradycardia, in which several authors * have reported partial syncope without pain.

The older age distribution of this group together with its high incidence of preceding coronary artery disease and cardiac hypertrophy may well be related to a high incidence of preceding congestive failure or of a latent tendency to it. This in turn may account for the prevalence in this group (10 of 21 cases) of predominant dyspnea and no pain. Other authors † have shown that the commonest type of acute infarcation without pain is that in which there is an acute exacerbation of preceding, usually mild, failure with severe dyspnea. Papp [9] makes note of a reverse situation; in his cases without dyspnea and failure pain was always present. The three cases with dyspnea and pneumonia were probably dyspnea with failure and superimposed infection. The three cases with predominant middle or lower abdominal pain could be explained on the basis of visceral congestion secondary to infarction and right heart failure.

The lower incidence of positive associated laboratory and clinical findings may have resulted in part at least from a less intensive work up, as the diagnosis was not suspected clinically in any of these cases except one prior to the findings of diagnostic electrocardiographic findings.

The third, or silent, group presents the most difficult problem in rationalization. We cannot explain these cases solely on the basis of mental deterioration, as only one had gross deterioration. Personal interview and discussion with resident physicians, nurses, social worker, and psychiatrist regarding these cases revealed no remarkable difference from the rest of our population in the degree of memory impairment or personality structure. However, the inevitable temporal difference in this totally asymptomatic ambulatory group who were picked up on routine electrocardiograms or those taken for reasons other than a suspi-

* References 8-10.

† References 9, 11, and 12.

cion of infarction may have contributed to the forgetting of minor upsets, which with impaired memory may in fact have represented typical or atypical symptoms of acute infarction. This wider span between the baseline and initial abnormal electrocardiogram of from weeks to months may also have contributed to the lower incidence of positive associated laboratory and clinical findings.

In spite of this considerable factor of error, such a large proportion of silent cases needs additional explanation. One explanation would rest on the assumption that they were similar to those cases described by Blumgart [13] with healed infarcts at postmortem examination and a negative clinical history. He feels that a considerable collateral circulation may have been established before the final occlusion of a main coronary artery, permitting the continuation of life with healing of the infarcted area. However, he offers the alternative explanation that they may represent the coalescence of many small areas of fibrosis consequent to repeated focal myocardial ischemia.

Herrick [14] hypothesized that gradual progressive coronary artery narrowing may result in a relatively anesthetized area owing to destruction of nerves, vessels, and muscles, so that a new obstruction results in no pain being appreciated.

Keefer and Resnik [15] feel that in a subject relatively insensitive to pain or suffering from a very slow infarctive process, with only a few fibers being injured at a time, the resulting sensation is insufficient to reach the sensorium and cause the sensation of pain.

We attempt to exclude cases where gradual myocardial fibrosis secondary to coronary sclerosis over a long period of time may cause changes similar to those of acute infarction by our criteria of exclusion, and in most of our cases the intervals between electrocardiograms were too short for this explanation.

The best explanation may be the relative increase in insensitivity to pain as well as other sensations in the aged, the increase in memory loss in the aged, and, in addition, as noted by Marchand [6] in psychotic patients, a partial loss of the meaning of pain sensation. In addition, the older patient has an attitude towards disease which leads him to minimize or ignore symptoms, especially those of minor intensity.

Any comparison of the literature on this subject is made difficult by the special nature of this group and its limitation to nonfatal ambulatory cases. In any case, as pointed out by Roseman [16] in a recent review article, the literature on this subject is in a most confused state, owing to differences in the definition of silent infarction, the definition of pain itself, the methods of diagnosis and evaluation of clinical and postmortem material, and the types of population studied. The more recent material confining itself to acute general hospital material, a very selected group of very sick people and in a lower age range, reports a low incidence of painless infarction.

With specific reference to the aged, Littman and Barr [17] have described a condition they term acute atypical coronary insufficiency. This they associate with widespread coronary artery disease in the aged. It is marked by pain unrelated to effort and longer than 15 minutes in duration, fever, slight leucocytosis, and increase in the sedimentation rate without failure or shock. The electrocardiogram is often normal on admission and then slowly over days or weeks when the patient is asymptomatic develops symmetric T-wave inversions of indefinite subsequent duration. This syndrome they attribute to small and obscurely located myocardial infarctions. Some of our typical cases ran a somewhat similar course.

Gorham and Martin [12] and Kennedy [18] found their cases of infarction without pain to be older and to have a high incidence of dyspnea.

Adams [19] notes the frequency of infarction in the aged without obvious fresh thrombosis and with subendocardial necrosis with atypical symptoms.

Levy [20] illustrates a case with the onset and regression of marked serial electrocardiographic changes similar to those seen in some cases without any symptoms or signs, which he attributes to gradual coronary occlusion in cases with an adequate collateral circulation and with subsequent improvement in the collateral circulation.

Fagin and Chapnick [21] analyzed a group of 100 ambulatory labor union members over a two-year period in a manner somewhat similar to ours. They found seven who were completely asymptomatic. Their atypical group, of 41 cases, included 7 who correspond to our atypical group in the absence of angina or other pain sensation. This smaller incidence of silent and atypical infarctions as defined by us can be explained by the fact that theirs was a much younger series, only 2% over age 70 as compared with 80% over age 70 in our group and by the fact that they dealt with a clinic group and we with an institutional population.

Summary and Conclusions

In a group of 700 ambulatory aged men and women studied over a five-year period 51 cases of presumptive nonfatal myocardial infarction were diagnosed.

This series showed a high incidence of cases without pain or any other symptoms referable to myocardial infarction [16] and of cases without pain but with other symptoms referable to myocardial infarction.[21]

The groups with pain, without pain but with other symptoms, and without any symptoms were compared as to clinical, laboratory, and electrocardiographic findings.

The atypical symptoms were attributable to congestive failure, cerebral anoxemia, and visceral congestion, in that order of frequency.

The diagnosis was made correctly on clinical grounds prior to electrocardiographic interpretation in all of the typical cases, only one of the atypical cases, and none of the silent cases.

There is a high incidence of painless myocardial infarction in the aged of a relatively mild degree of clinical severity, which may be explained by the characteristics of this group with respect to coronary artery disease, cerebral arteriosclerosis, memory function, loss of the meaning of pain sensation, and the mental attitude of the aged patient toward symptoms of disease.

Routine electrocardiographic examination of the aged will uncover, in appreciable number, changes of major degree compatible with myocardial infarction which may be unsuspected clinically.

Acute myocardial infarction should be suspected and sought for among the aged who show unexplained behavior changes, sudden signs of cerebral insufficiency, or unexplained abdominal complaints or who develop an abrupt fall in blood pressure with or without preceding surgical procedure.

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Respiratory Manifestations of Chicken Pox

Special Consideration of the Features of Primary Varicella Pneumonia

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That chicken pox is not invariably a mild, uncomplicated exanthem of childhood is better recognized now than it was in the past century, when it was thought that, because of its benign course, the disease was of clinical importance only because it could be confused with smallpox.[1] The presence of disseminated visceral lesions in varicella neonatorum emphasizes the fact that this may be a severe and even fatal infection.* The commonest complication of chicken pox is secondary bacterial invasion of the skin lesions;[4] complications due to spread of the virus occur, however, and may produce even more serious problems, particularly since the responsible agent is not susceptible to any of the presently available antibiotic drugs.

Involvement of the respiratory tract during the course of chicken pox results either from secondary bacterial invasion or from extension of the viral infection. Pulmonary lesions in varicella have generally been regarded as uncommon and until recently were considered [5] to be entirely of bacterial origin, although "laryngeal ulcerations" due to chicken pox virus have been presumed to be a prediposing cause.† In a recent paper,[8] describing a single case of primary varicella pneumonia, it was stated that only 15 instances of this disease have been recorded in the world's literature.

Within the year we have observed five patients who developed pneumonia during the course of varicella. Because of this experience, all of the cases of chicken pox admitted to the Haynes Memorial Hospital from 1944 to 1955 were reviewed. The purpose of this paper is to report the results of this study and to characterize, on the basis of our own cases and those described in the literature, the clinical and the laboratory features of the pulmonary complications of varicella.

Methods

All patients with varicella who had respiratory symptoms at the time of admission to the hospital or who developed them subsequently were included in this study; in addition, there were a few persons who showed no clinical evidence of respiratory tract involvement but had pulmonary infiltration demonstrable on roentgenogram. A complete physical examination was carried out at the time of admission and repeated frequently throughout the acute phase of the illness. Complete blood cell counts, cultures of the nasopharynx and available sputum, and blood cultures were made at the time of admission to the hospital and repeated on an average of every two or three days, depending on the clinical situation. The lungs were examined by x-ray at the time of hospitalization if pulmonary involvement was suspected; roentgenograms were taken at least once before discharge. In those with severe pulmonary disease, x-ray examination was carried out twice a week; whenever possible, these patients were seen at periodic intervals for several months after discharge from the hospital. Blood electrolyte determinations and electrocardiograms were made whenever indicated.

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* References 2 and 3.

† References 6 and 7.

Results

Four hundred fifty-three patients with varicella were admitted to the Haynes Memorial Hospital between 1944 and 1955. Respiratory tract involvement varying from mild tracheobronchitis to severe pneumonia occurred in 41, or 9%. The age of the patients ranged from 4 days to 65 years; 50% were 6 years old or less; 25% were between 6 and 18 years, and 25% were between 19 and 65 years of age. A large number were pupil nurses and college or medical students who were hospitalized primarily for isolation purposes and not because of the presence of complications.

The patients with respiratory tract complications were from 7 months to 49 years old and, on the basis of age, were distributed into two widely separated groups. There were 20 persons younger than 7 and 21 older than 19 years; there were none between these two age ranges. The absence of respiratory manifestations among cases in this gap was not related to the age distribution of the group as a whole. Involvement of all parts of the respiratory system from the larynx to the pulmonary parenchyma was noted and was of two etiologic varieties, bacterial and nonbacterial, which included all instances of "primary varicella pneumonia."

Bacterial Infections of Respiratory Tract

Characteristically, bacterial infections of the respiratory tract occurring during varicella first appeared after defervescence from the chicken pox had taken place. The onset of symptoms was abrupt, with a rapid secondary rise in temperature and an elevation of the peripheral white blood cell count, with a predominance of neutrophiles. Pathogenic bacteria were isolated from the nose, throat, or sputum in almost every instance; bacteremia was never encountered. Roentgenographic changes in the lungs were relatively nonspecific in nature, except in cases with lobar consolidation, and generally indicated the presence of basilar brochopneumonic infiltration. It was not possible in every instance to make an absolute distinction between viral and bacterial infections of the respiratory tract during the course of chicken pox, even when these criteria were employed.

Respiratory complications of bacterial origin in chicken pox were observed only in children; no patient was older than 7 years, and the youngest was 7 months of age. A total of 222 patients with varicella were 7 years old or less; 15 of these (6.8%) were found to have either tracheobronchitis or pneumonia, presumably due to bacterial infection. Approximately 50% of the secondary infections were in patients less than 3 years old.

Pathogenic organisms were recovered from the nasopharynges of 11 patients; four revealed mixtures of nonpathogenic bacteria. The commonest pathogen found in children was Hemophilus influenzae (six cases); it was more frequent than β-hemolytic Streptococcus (four patients) or Pneumococcus (one case). H. influenzae was recovered in four instances of pneumonia; three were attributed to β-hemolytic Streptococcus; Pneumococcus in association with the influenza bacillus was demonstrated in one person with pneumonitis.

The white blood cell count was 12,000 per cu. mm. or higher in all but one patient (a 19-month-old child with a WBC count of 7400 per cu. mm.). Most of the cell counts were between 15,000 and 20,000 per cu. mm., the highest being 32,000, in a case of lobar pneumonia. Neutrophiles constituted 75% or more of the white blood cells in every instance.

Roentgenographic study of the lungs revealed a predominant picture of peribronchial and parenchymal infiltration in 12 cases and lobar consolidation in 2.

In the patients with tracheobronchitis the onset of symptoms was abrupt, with a rapid secondary rise in temperature to between 101 and 104 F. Cough, tachypnea, sternal retraction on inspiration, "croup," and, in some instances, cyanosis were present. Penicillin, combinations of penicillin with streptomycin or a sulfonamide, or sulfona-

mides alone were administered, depending on the bacteriologic findings. This therapy resulted in rapid recovery with early defervescence and disappearance of the pathogenic organisms from the respiratory tract. With the temperature varying between 101 and 104 F, cough, tachypnea, retraction of the intercostal spaces, diminished breath sounds over the affected pulmonary area, and, in some patients, dullness to percussion were noted in the cases of secondary bacterial pneumonia. Antibiotic therapy was selected on the basis of the predominating organism and produced rapid recovery; one patient, however, developed a pleural effusion during the course of pneumonitis due to β-hemolytic Streptococcus.

Nonbacterial ("Viral") Infections of Respiratory Tract

The diagnosis of "viral" infection of the respiratory tract during the course of chicken pox was based on the presence of such features as slow onset of symptoms, paucity of physical findings in relation to the degree of respiratory embarrassment, normal or slightly elevated white cell count, and the absence of bacterial pathogens from cultures of nose and throat. In those cases in which elevated white blood cell counts, rapidly rising temperature, and pathogenic bacteria in the nasopharynx were present, the viral etiology was suspected primarily on the basis of the x-ray appearance of the lungs and the evidence produced by others [5] that these findings may be present when the agent of chicken pox invades the lungs. A case in point is the one described by Waring and Neuberger [5]: their patient had high-grade fever, leucocytosis with a predominance of neutrophiles, and pneumococci in the sputum as proved by mouse inoculation. The changes visible upon x-ray were interpreted as being consistent with diffuse and extensive viral pneumonitis and consisted of numerous fluffy rounded infiltrations scattered throughout the entire lung field but more densely situated at the bases. There was also marked reticulation of the lung, indicating interstitial changes. The validity of the clinical impression of a viral infection of the lung was confirmed by postmortem study. Consolidation without suppuration was observed on gross inspection, and the following microscopic changes were recorded: (1) epithelial exfoliation of the trachea and bronchi and a mononuclear cell infiltrate in the submucosa, (2) swollen alveolar septal cells associated with interstitial edema and capillary engorgements, and (3) alveolar exudate composed of epithelial cells, red cells, and fibrin, in some areas; where there was condensation of the fibrous exudate, a hyaline-like membrane could be seen. Polymorphonuclear cells were conspicuously absent.

"Viral" infections of the respiratory tract developing during the course of varicella were observed primarily in adults, but they were not restricted to this age group. Five of the patients were under 2 years of age. Twenty-one were more than 19 years old; of these, 14 were considered to have primary varicella pneumonia on the basis of the roentgenographic changes in the lungs. Because of differences in site of infection, severity, and extent of involvement, the clinical manifestations of complicating viral respiratory disease in chicken pox have been divided into three types.

Type I Viral Respiratory Involvement.—There were five children in this group; all had clinical findings consistent with acute laryngotracheobronchitis early in the course of chicken pox. The respiratory disease was mild and subsided rapidly without specific therapy. The white blood cell counts were normal or slightly low, the highest being 8200 per cu. mm.; the differential counts were normal except in two instances in which transient eosinophilia appeared. Cultures of the upper respiratory tract revealed only normal microflora. The temperature ranged from 100.8 to 104 F. Moderate to severe cough was present. In the patients who were severely ill and had tachypnea and sternal retraction, recovery took place in about 24 hours, the only treatment being moist nebulized oxygen. X-ray study in four of

the youngsters revealed hilar adenopathy with peribronchial thickening extending to the bases; one had evidence of mild bronchopneumonia. In general, the clinical features of this type of tracheobronchitis did not appear different from those observed in children with this disease who do not have varicella.

Type II Viral Respiratory Involvement.—Seven patients ranging in age from 19 to 48 years, five males and two females, were included in this group. In each instance, the reason for admission to the hospital was the presence of a severe rash, high temperature, and distressing cough. The patients in this group were more severely ill than those in Type I. Although one had a normal temperature during the entire course of the disease, the others had temperatures from 102 to 105 F. The varicella eruption was extremely widely distributed in all but two cases; in one, the rash was hemorrhagic at the time of first appearance of respiratory symptoms. One patient had a severe conjunctivitis, and another developed iritis at the height of the eruption. Clinical manifestations of the respiratory disease as well as the roentgenographic changes were variable. X-ray study revealed only peribronchial thickening with hilar enlargement in some cases; in others there was definite peribronchial infiltration, and one exhibited widespread interstitial pneumonia. The symptoms were not directly related in severity to the extent and character of the x-ray changes. One patient who had severe dyspnea and cyanosis revealed very little change in the lung fields; another who showed extensive interstitial infiltration had a remarkable paucity of respiratory manifestations. Coarsening of the breath sounds was the only unusual physical finding and was not present in every case. The peripheral white blood cell count ranged from 4200 to 15,000 per cu. mm. Study of the nasopharyngeal microflora revealed pathogens in only two patients; the organism was H. influenzae. There was no correlation between the level of the white blood cell count and the presence or absence of pathogenic bacteria in the respiratory tract.

Uneventful recovery, without the use of specific antimicrobial therapy, occurred in all but one patient, an elderly woman who died of intractable acute cardiac failure and shock; necropsy revealed a mild pneumonitis with the anatomic features of a viral infection. In most instances the changes in the lungs observed by x-ray cleared much more slowly than the clinical manifestations. Marked peribronchial infiltration was noted to persist for about one month after discharge from the hospital in one case.

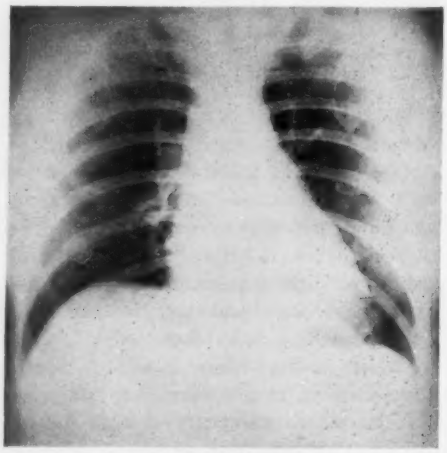

Fig. 1.—A 46-year-old woman, whose chest roentgenogram shows a moderate peribronchial infiltration characteristic of Type II viral pneumonitis, died on the sixth day of an illness characterized by rapid onset of high fever in association with a widespread vesicular rash. As the rash became hemorrhagic, dyspnea, tachypnea, and moderate cyanosis appeared. Death occurred as a result of acute congestive failure and shock. At autopsy lesions were found throughout the body and were prominent on the pleurae. The lung parenchyma was the site of interstitial edema with a moderate mononuclear infiltrate.

Figure 1 illustrates Type II viral respiratory infection in varicella.

Type III Viral Respiratory Involvement.—The patients included in this group were those whose main complaint was of respiratory distress of varying severity. These are the cases classified as severe and un-

questionable primary varicella pneumonia. The average age of this group was higher than that of Type II: Four of the patients were 22 to 29 years old; seven were 30 to 40 years old, and three were more than 40 years old. Eight of the patients were women.

All of the patients had very extensive, almost confluent vesicular eruptions which covered the face, trunk, extremities, palms, and soles. The clinical picture was often suggestive of variola, because of the presence of high-grade fever, umbilicated lesions, marked facial and palmar rash, and severe back pain, particularly during the prodrome. Vesicles were commonly present on the soft palate, buccal mucous membrane, and pharynx. Severe conjunctivitis was observed in several instances. One patient had a hemorrhagic rash. The temperature ranged between 101.2 and 105.4 F rectally.

Cough was a major symptom in all but one patient and was dry or productive of thick secretions. In three cases the sputum contained bright red blood; gross hemoptysis was not noted. Chest pain was present in 50% of the group and was either pleuritic in character or experienced as a sensation of "tightness" constricting the chest, noticeable especially with deep inspiration or coughing. Dyspnea was present in half of the group, while all exhibited tachynea, the respiratory rate ranging from 24 to 76 per minute. Prolongation of the expiratory phase of respiration was common (50%). Physical examination of the lungs was not very remarkable; the only noticeable changes were coarsening of the breath sounds and the presence of rhonchi and expiratory wheezes. Physical evidence of pulmonary consolidation was not detectable. Cyanosis was noted in four cases.

White blood cell counts made at the time of entry to the hospital and twice weekly thereafter were in the range of 9000 per cu. mm., with a slight lymphocytosis. In two cases the white blood cell counts were 15,000 and 18,000 per cu. mm., respectively; in two, a pharyngitis due to the β-hemolytic Streptococcus was present. Bacteriologic studies of the pharynx or sputum revealed Streptococcus pyogenes in two patients, H. influenzae in three, and mixtures of nonpathogenic bacteria in the others. Five of the patients had received various antimicrobial agents prior to hospitalization, without any affect on the pulmonary disease.

The x-ray pictures of the chests of all the patients were remarkably similar and showed numerous fluffy slightly rounded infiltrations scattered diffusely throughout both lungs. The lesions were concentrated most heavily in the bases; their size and shape were variable and their outlines indistinct. Hilar lymphadenopathy and prominence of bronchovascular markings were universal. The roentgenographic changes appeared to be diagnostic of primary viral pneumonia in varicella.

The duration of severe illness varied from one day to two weeks, during which dyspnea, cough, extensive skin eruption, and high temperature were striking. Seven of the patients were afebrile after 36 hours; three maintained fever for 5 days, and two did not defervesce until 2 weeks after entry to the hospital. The use of oxygen relieved dyspnea and cyanosis regularly and rapidly. The severity or persistence of symptoms were not always correlated with the height of the temperature or the extent of the pulmonary lesion as demonstrated by x-ray. For example, a woman with severe dyspnea and tachypnea had a temperature of only 101 F, while a man with high-grade fever (105 F) had few pulmonary symptoms. Two patients required longer than a week to recover; one had orchitis and the other had successive crops of new skin lesions erupting over 11 days.

Seven patients with Type III pulmonary involvement were treated with various antibiotic agents, including the tetracyclines, in large doses; in some the possibility of bacterial infection was suspected, while in others an attempt was made to determine whether the drugs might be of value despite the viral nature of the lesion. The clinical and roentgenographic course of the disease was the same in treated and untreated cases.

A number of "complications" appeared in this group of patients. Four developed a psychosis. Unilateral iritis occurred in one case. Severe conjunctivitis was common. Orchitis appeared in one person with an extensive pulmonary lesion; this case has been reported previously.[10] Meningomyeloencephalitis was observed in one patient.

Figures 2 and 3 illustrate Type III viral respiratory infection in varicella.

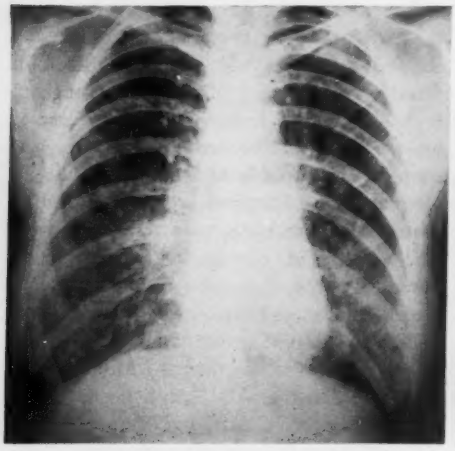

Fig. 2.—A 39-year-old woman entered the hospital because of severe respiratory distress. Examination revealed a temperature of 103 F, a diffuse vesicular rash characteristic of chicken pox, rapid labored respiration, harassing cough, and diffuse inspiratory rales and wheezing over both lung fields. Recovery from most of the symptoms occurred in about three days. This Figure illustrates the roentgenographic changes present in the lungs at the time of admission to the hospital.

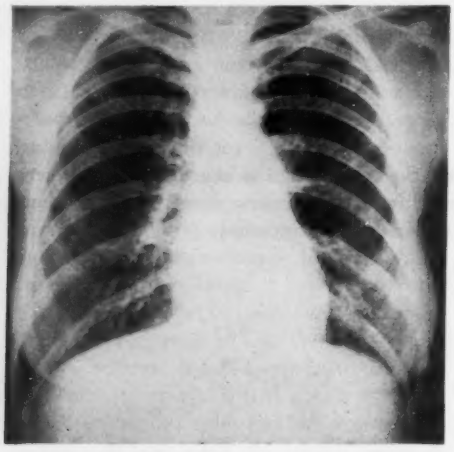

Fig. 3.—Same patient as in Figure 2. X-ray taken six days after the first.

Clinical-Laboratory Features of Primary Varicella Pneumonia

Including the patients reported in the present paper, there appears to be a total of 29 cases of severe pulmonary involvement, primary virus pneumonia, occurring during the course of chicken pox and probably due to infection of the lungs by the virus of this disease. Fourteen patients were seen by us; only those classified as Type III are included, because those considered to be Type 1 had only tracheobronchitis and of those labeled Type II all but one showed only peribronchial infiltration on roentgenographic investigation. Sixteen other cases have been recorded in the literature;‡ of these, one [10] was also studied by us. An analysis of the important findings in the entire group is presented below.

TABLE 1.—*Age Distribution of Ptinsetwitha Varicella Pumenonia*

Age, Yr.	Patients, No.
19-30	8
30-40	15
40-50	5
71	1

Sex and Age.—Seventeen (58.6%) of the patients were males. The age distribution is presented in Table 1.

Clinical Manifestations.—Manifestations of involvement of the respiratory tract appeared in less than five days after the rash of varicella was first noted, in most instances. In one case pulmonary disease developed prior to the eruption, while in two others it was delayed until 7 to 10 days after the first vesicles became apparent. All but one of the patients had fever. Cough of varying character and severity was always present; in 50% of the cases it was

‡ References 5 and 8-18.

dry, while in the others moderate to large quantities of sputum were produced. Blood-tingeing of the sputum has been noted; hemoptysis of as much as a cupful has been recorded.[5] Chest pain occurred in one-quarter of the patients and was substernal, constrictive, or pleuritic in character. Dyspnea, cyanosis, and tachypnea were very common.

As has been pointed out previously,[9] physical examination of the lungs revealed little of note despite the severity of the symptoms in many of the patients. In general, percussion over the chest was resonant, the breath sounds were normal in intensity and character, and rhonchi and wheezes but no rales were present. In cases with marked infiltration, particularly in the bases of the lungs, dullness to percussion and diminished breath sounds were noted.

The skin eruption was extensive and severe in all cases and hemorrhagic in four; in two of the latter, death occurred. A summary of the clinical mainfestations of primary varicella pneumonia is presented in Table 2.

TABLE 2.—*Clinical Manifestations of Primary Varicella Pneumonia*

Symptom or Sign	Patients, No.
Dyspnea	23
Tachypnea (30-80 per minute)	20
Cyanosis	21
Hemoptysis	10
Chest pain	9
Hemorrhagic skin lesions	4

Laboratory Findings.—In 10 of the 29 reported cases the total white blood cell count was 4000 to 7000; in 11 it was 7000 to 12,000, and in 6 it was higher than 15,000 per cu. mm. In all but five of the patients the percentage of neutrophiles was 70 or less.

Thrombocytopenia without clinical evidence of a defective clotting mechanism was noted in one patient.[9] Despite the presence of hemorrhagic skin eruptions in some of the patients, platelet deficiency or abnormal coagulation of the blood was not detected.

Among the pathogenic bacteria present in the nasopharynx or sputum of these cases were H. influenzae in three, β-hemolytic Streptococci in three, and pneumococci in two.

The roentgenographic changes in the lungs in all of the patients were remarkably similar. All had widespread floccular densities, densely reticulated markings, and heavy peribronchial infiltrations. The appearance of the x-ray picture was striking enough to suggest that, in cases of chicken pox, it was diagnostic of primary viral pneumonitis. Similar changes may be seen, however, in miliary pulmonary tuberculosis or in other acute exudative diseases of the lungs.

Response to Antibiotic Therapy.—All but seven of the patients were treated with one or more antibacterial agents: Some received only a sulfonamide; others were given penicillin, while still others were treated with one of the tetracycline derivatives. The commonest reason for therapy was inability to decide whether or not the pulmonary lesion was due to bacterial or viral infection. In other instances, the antimicrobial drugs were given for the purpose of prophylaxis. In some cases recovery appeared to be rapid following the exhibition of chlortetracycline. However, response to treatment has been variously interpreted.[12] In seven patients we withheld treatment; rapid and uneventful recovery occurred in every instance. When the course of the pulmonary disease in these patients was compared with that in those who had received chlortetracycline, no significant difference was apparent.

Outcome of Varicella Pneumonia.—Four of the twenty-nine patients with pulmonary complications occurring during the course of chicken pox died; one had encephalitis,[5] one succumbed to heart failure,[14] and two died as the result of overwhelming viral infection.

Comment

In a study of more than 2500 patients with varicella, Bullowa and Wishik [4] found 21 instances of pneumonia; in 20, β-hemoly-

tic Streptococcus was demonstrable. No mention is made, however, of the age of the patients. In another investigation of 775 cases, only 4 instances of bronchopneumonia were detected.[19] The incidence of pulmonary complications of varicella reported in these two series is appreciably smaller than that noted by us; respiratory manifestations due either to bacteria or to the virus of varicella appeared in 8.6% of 453 cases. In the group as a whole, nonbacterial pneumonitis appeared in 5.1%, but in adults the incidence of this type of disease was 16.5%. There may be two reasons for the discrepancies in incidence in other studies and ours: 1. A relatively large number of adults were included in the present study; 25% were older than 18 years. Since nonbacterial pneumonia occurred in adults, this may account for the relatively large number of cases of pulmonary involvement reported in this paper. 2. The vast bulk of patients with uncomplicated varicella are not admitted to the hospital. This probably resulted in a disproportionate number of complicated cases in our group, some of which were hospitalized because of respiratory disease.

Although our studies indicate that primary varicella pneumonia is much commoner in adults than in children, those in the younger age group are not immune to the development of this complication. Oppenheimer[2] demonstrated a patchy consolidating pneumonia in a newborn child who succumbed to varicella; Johnson[20] recorded a probable varicella pneumonia in a child. In the present series, secondary bacterial infection appeared to be responsible for all of the pumonary lesions observed in children. On the other hand, adults seemed to be particularly resistant to invasion of the lungs by bacteria but developed pneumonia due to the virus of varicella with relative ease.

Neither autopsy studies nor clinical observations clearly indicate the pathogenesis of the pneumonia of chicken pox; the anatomic features of the pulmonary lesions as they appear at autopsy together with the clinical course of the disease suggest, however, what is the probable sequence of events. In the esophagus and bronchi, as on the skin, rarefaction of the cytoplasm and vacuolation of epithelial cells characterize the first response to the invasion by the virus of varicella. The progression of the disease from the earliest lesion to the full-blown pneumonia is in many respects similar to that which occurs as the eruption on the skin develops. The lesions within the tracheobronchial tree multiply; the reaction in the tissues adjacent to them increases, and mononuclear cells infiltrate the subepithelial layers. Superficial cells are exfoliated and form a bronchial exudate to which red cells may be added from ruptured capillaries. Smaller bronchioles may be occluded both by the exudate formed about them and by hypertrophy of their lining epithelium. It is probable that in most instances of mild infection the reaction to invasion by the virus is limited to the bronchi and peribronchial tissues. In very severe cases interstitial infiltration is so widespread that its origin from within the bronchi does not seem probable. A widespread interalveolar reaction seems more likely; changes are present within the septal cells, interstitial infiltration is apparent, and characteristic intranuclear inclusions are demonstrable in the epithelial cells. Pleural lesions have been noted in several cases; these are probably responsible for the production of pleuritic pain. Although the process which has been described thus far is an interstitial one, consolidation of lung occurs as a result of bronchial obstruction and the formation of alveolar exudate. Depending on the extent of the pneumonic process, the roentgenogram may reveal only hilar adenopathy and prominence of bronchovascular markings or a widespread pulmonary infiltration. The clinical and x-ray differences detected in the pneumonia of nonbacterial origin in chicken pox appear to be related entirely to the degree and extent of anatomical involvement and not to etiology.

Summary and Conclusions

In a group of 453 patients with chicken pox, disease of the respiratory tract was noted in 41.

Of 41 patients with respiratory tract infection in varicella, 20 were less than 7 years old and 21 were over the age of 19 years.

Bacterial infections of the respiratory tract occurred only in children and were due most often to Hemophilus influenzae; viral disease of the respiratory tract was also present in the young age group.

The viral infections of the respiratory tract in varicella have been classified into three types on the basis of the extent and severity of involvement; Type III, the severest, includes all cases of primary varicella pneumonia.

Pulmonary disease due to bacteria was not observed in adults with chicken pox; in all instances, the respiratory infections appeared to be of viral origin. Primary varicella pneumonia occurred only in adults.

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Treatment in Internal Medicine

TREATMENT OF ADDISON'S DISEASE

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ONE HUNDRED years has elapsed since Thomas Addison published his epochal report "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules."[1] The remarkable progress of medical science in the past century is in no way better exemplified than by the advances that have been made in our knowledge of the effects and the treatment of adrenal insufficiency. Although there is still much to be learned of the normal and pathological physiology of the adrenal glands, from the practical viewpoint of therapy their destruction or removal no longer presents a danger to life or even to normal health.

These advances have been made possible by a remarkable series of collaborative enterprises among biochemists, physiologists, and physicians during the past 30 years. Prior to this era of collaboration attention had been directed principally to the development of extracts of adrenal glands to provide replacement therapy. Sir William Osler, in 1896,[2] was the first to report the successful maintenance of life in a patient with Addison's disease by the use of glycerin extract of fresh hog adrenal which he collected and processed himself. Not until 30 years later, however, did adrenal extracts become of practical therapeutic importance, largely through the efforts of Hartman,[3] Rogoff,[4] and Swingle and Pfiffner.[5] At about the same time the importance of salt replacement was established by Loeb[6] and independently by Harrop[7] and the first steps in the conquest of Addison's disease were accomplished.

The final stages of this victory began with the isolation and synthesis of desoxycorticosterone by Steiger and Reichstein,[8] in Switzerland, and the identification and characterization of the various corticosteroids by Kendall[9] at the Mayo Clinic. With the synthesis of 11-dehydro-17-hydroxycorticosterone by the Merck company on a commercial scale in 1949, the triumph over Addison's disease became complete. The various refinements in therapeutic techniques since then may be considered in the nature of mopping-up operations; they are nonetheless of great importance to the patient.

Hormone Preparations Available

1. Primarily Carbohydrate-Regulating Glucocorticoids

(a) Cortisone (11-Dehydro-17-Hydroxycorticosterone).—This synthetic steroid is available in scored 25 mg. tablets and as a saline suspension containing 50 mg. per milliliter. It was the first and is still the most widely used of the carbohydrate-regulating hormones, and its value in replacement therapy is firmly established.

(b) Hydrocortisone (11-17-Dihydroxycorticosterone).—The action of this substance is in all respects qualitatively similar to that of cortisone. It is about 20% more potent than cortisone on a weight-for-weight basis, and there is evidence that it is the actual glucocorticoid secreted by the adrenal. Hydrocortisone is available for oral use as the acetate in scored 10-mg. tablets and for intravenous use as a 0.5% solution in 50% alcohol. This solution is put up in 20 ml. ampules, each containing 100 mg., which is diluted to 500 or 1000 ml. before intravenous administration.

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For oral use hydrocortisone has no advantage over cortisone in the treatment of Addison's disease except for its slightly greater potency. Its most important use is in the emergency intravenous treatment of the acute Addisonian crisis. It also has the unique advantage of exerting a local anti-inflammatory effect when applied directly at the site of inflammation.

(*c*) (*Prednisone Meticorten; Δ-1-Cortisone) and Prednisone (Meticortelone; Δ-1-Hydrocortisone).*—By removal of trim-hydrogen from carbons 1 and 2 and rearrangement of the internal structure of ring 1 in the basic steroid nucleus of the glucocorticoids, the carbohydrate-regulating effect has been increased approximately five-fold while the salt-retaining effect is either unchanged or may be even diminished as compared with cortisone and hydrocortisone. Although of great value in conditions where an anti-inflammatory action is desired without the side-effect of salt retention, prednisone provides no particular advantage in the treatment of Addison's disease where salt-retention is desirable. At present this substance is as much more expensive as it is potent in comparison with the other steroids. If and when its price is reduced, the greater potency may result in a significant economic advantage to the Addisonian when used in conjunction with the salt-retaining hormones. Prednisone is at present available in 5.0 mg. scored tablets.

2. Primarily Salt-Retaining Hormones (Mineralocorticoids)

(*a*) *Desoxycorticosterone.*—The activity of this compound is principally one of salt retention. It is available in the form of its acetate for intramuscular or sublingual use or as pellets of 75 to 125 mg. for subcutaneous implantation. In the form of its trimethyl acetate in saline suspension it may be used intramuscularly to provide a slowly absorbed deposit of hormone with continuous release of activity for periods up to one month. Desoxycorticosterone is not absorbed from the gastrointestinal tract.

(*b*) *Fludrocortisone Acetate (Florinef; 9α - Fluoro - 17 - Hydroxycorticosterone - 21 - Acetate).*—The addition of an atom of fluorine at the 9 position in the steroid nucleus has resulted in an extraordinary increase of potency, approximately 5 times the salt-retaining effect of desoxycorticosterone and 20 times the carbohydrate-regulating effect of hydrocortisone. Moreover, the effect of a single dose is maintained for a full 24 hours.[10] Fludrocortisone acetate is readily absorbed from the gastrointestinal tract, and the administration of 0.1 to 0.2 mg. daily by mouth will provide complete replacement therapy for adrenalectomized persons in respect to the salt-retaining hormone. Complete carbohydrate regulation cannot be achieved with this substance alone without producing excessive salt retention and hypertension, but the combination of it with a maintenance dose of glucocorticoid has enormously simplified the management of patients with Addison's disease, and this combination promises to be the treatment of choice for the future.

Recently there has been isolated from normal urine a steroid with very potent salt-retaining activity. This substance is characterized by an aldehyde group on C 13 in resonance with a hydroxyl on C 11. It has been termed aldosterone and is presently considered to be the actual salt-retaining hormone produced by the adrenal. It has been shown, however, to be no more potent than fludrocortisone and does not have as long a duration of action.

Institution of Therapy

1. Patients in Addisonian Crisis

When the diagnosis of adrenal insufficiency is made in a patient who presents himself critically ill in the vascular collapse characteristic of an Addisonian crisis, therapy must be prompt and vigorous. The following outline may provide a guide.

(*a*) *First Day.*—A continuous intravenous infusion of 2000-3000 ml. of 5% dextrose in saline containing 100 mg. of dihydrocorticosterone per liter should be started at once. The total volume of fluid

must depend on the degree of shock and dehydration and the state of the cardiovascular system as observed in each individual patient. The quantity of hormone given, however, should never be less than 200 mg. in the first 24 hours. This quantity will ordinarily provide an adequate salt-retaining as well as carbohydrate-regulating effect, but it is advisable to administer in addition 5 mg. of desoxycorticosterone intramuscularly except in older patients or those with cardiovascular disease.

It is of particular importance to remember that the effectiveness of intravenous hydrocortisone depends even more on the duration of administration than on the total amount administered. Only minute quantities can be utilized at any given instant: anything in excess of this amount will be metabolized and excreted. Thus, intravenous therapy should usually be continuous during the first 24 hours, because the patient may relapse into shock within 4 to 6 hours after cessation unless he is supported by oral or intramuscular administration of hormone, which provides a more gradual rate of absorption. Oral therapy is preferable to intramuscular because absorption is faster by the oral route and higher blood levels are obtained. Hormone injected intramuscularly is absorbed at such a slow rate that it requires a longer time and a larger initial dose to build up an effective blood level, although once this is achieved the gradual absorption of the intramuscular deposits provides a duration of action of 12 to 24 hours or longer.

Epinephrine, 0.3 mg. subcutaneously, or levarterenol (Levophed), 2γ to 4γ per minute intravenously, may be given initially in patients with profound vascular collapse, but these measures are rarely necessary today because of the remarkably prompt response to the intravenous administration of hormone. The same may be said for the transfusion of blood, plasma, or human albumin unless there is external loss of these substances through hemorrhage. Ordinarily the patient will begin to show improvement within two to four hours after institution of therapy. It is often possible to start a high-carbohydrate liquid diet by the end of the first 8 to 12 hours.

As soon as possible after treatment is begun, the precipitating cause of the crisis should be determined and therapy inaugurated with antibiotics or other appropriate measures.

(*b*) *Second Day.*—Another 1000 to 2000 ml. of 5% dextrose in saline containing a total of 100 mg. of dihydrocorticosterone should be given over an 8- to 12-hour period. Frequent feedings with a bland high-carbohydrate diet may be started unless contraindicated by the condition precipitating the crisis, such as a surgical operation.

At least six hours before the end of this infusion, oral therapy with 25 mg. of cortisone every six hours should be commenced. If oral therapy is impossible or contraindicated, 50 mg. of hormone in saline suspension should be given intramuscularly according to the same time schedule.

(*c*) *Third and Subsequent Days.*—Most patients, by the third day, will be able to consume a normal diet and be maintained on oral cortisone, 25 mg. every six hours. This dose can be reduced subsequently by 25 mg. each day to the final maintenance level of 12.5 mg. twice daily by the end of a week.

Postoperative patients and those in whom the condition precipitating their crisis constitutes a continuing threat to their recovery may require a continuation of the same regimen as outlined for the second day until they are sufficiently improved to be able to consume a normal diet.

On the third day it is advisable to give a second dose of 2 mg. of desoxycorticosterone intramuscularly. Thereafter one of the various methods of providing salt-retaining hormone, to be discussed below, should be instituted.

2. Patients Not in Crisis

When the diagnosis of Addison's disease has been established by the appropriate diagnostic procedures [11] in a patient in whom the onset of symptoms has been gradual

and who is not critically ill, oral therapy may be started at once according to the following regimen:

(*a*) *Glucocorticoids.*—Cortisone, 25 mg., or hydrocortisone, 20 mg., is taken on arising and again after 6 to 12 hours for one week or until distinct improvement in strength, appetite, and sense of well being is observed. The dose is then reduced to 12.5 mg. of cortisone or 10 mg. of hydrocortisone given twice daily.

(*b*) *Mineralocorticoids.*—Until the development of fludrocortisone, replacement therapy consisted of the subcutaneous implantation of 1 or 2 pellets containing 125 mg. of desoxycorticosterone every 9 to 12 months, or the intramuscular injection once a month of 40 to 50 mg. of the trimethyl acetate of desoxycorticosterone in a saline suspension. These methods have been highly successful but have suffered from lack of flexibility and adaptability to the varying requirements of different persons and of the same person at different times.

The introduction of fludrocortisone has made it possible not only to supplant parenteral with oral therapy but also to adjust the dose much more accurately to fit individual needs. This potent hormone is capable of supplying adequate salt retention in doses varying from 0.1 to 0.2 mg. per day. Larger doses than this when given over prolonged periods of time may induce an excessive elevation of the blood pressure in patients with Addison's disease, particularly in those with a preexisting tendency to hypertension. Experience is as yet too limited to state with certainty the smallest effective dose, but it may quite likely be even lower than the figure of 0.1 mg. daily.

Although it is necessary to continue the use of cortisone or hydrocortisone in conjunction with the fluorine-containing compound, it is becoming apparent that in some cases adequate maintenance can be achieved with only one-half the previously indicated quantity of the glucocorticoids, namely, 12.5 mg. of cortisone or 10 mg. of hydrocortisone once daily.

It should be mentioned here that in a certain proportion of patients, especially those with relatively long-standing adrenal insufficiency, a period of several months may elapse before the full beneficial effect of therapy will become evident. Eventually, however, with adequate hormone replacement it is possible to restore a person with Addison's disease to a completely normal state of well-being.

Treatment of Complications

With the onset of stressful situations such as acute illness, trauma, or even physical or psychological fatigue, the requirement for the adrenocortical hormones is increased. The extra need can nearly always be met by increasing the dose of cortisone to 25 mg. three to four times daily, with gradual return to maintenance levels as the condition of stress subsides. If these larger doses of the glucocorticoids are required for more than three to four days, they should be supplemented with 1 to 2 gm. of potassium chloride daily in enteric-coated tablets. Ordinarily no increase in the maintenance dose of mineralocorticoids is necessary, but in complications associated with hemorrhage or hypotension from any cause it may be desirable to add an extra dose of 0.2 mg. of fludrocortisone acetate by mouth or 1 mg. of desoxycorticosterone intramuscularly once daily for a few days.

Patients with Addison's disease undergoing surgery should be given an extra oral dose of cortisone, 25 mg., 12 hours and immediately prior to operation, or twice this amount intramuscularly. With the commencement of anesthesia a continuous infusion of hydrocortisone in 5% dextrose should be started, running at the rate of 100 mg. of hormone over an eight-hour period. In major operations a second similar infusion of 100 mg. of hormone in 5% dextrose in saline is usually advisable. Thereafter the patient is treated as described above for second and subsequent days of recovery from an Addisonian crisis. With this treatment it is now possible to carry out virtually any necessary surgical pro-

cedure with impunity in patients with Addison's disease.

Complications of Treatment

Excessive doses of the adrenocortical steroids will cause all the same untoward side-effects in the Addisonian patient as they do in the normal person, but there is ordinarily a wide margin of safety between the dose producing adequate replacement and that causing symptoms of adrenal overactivity.

The commonest complication of therapy in the Addisonian patient side-effects hypertension due to excessive administration of salt-retaining hormone. These patients appear to be more sensitive than normal subjects to the action of this hormone, particularly to the hypertensive effect of the fluorinated compound. Frequent observations of the blood pressure should be made during the first few months of treatment until the optimum dosage schedule is established. The patient's weight should be followed carefully, and heart size should be determined from time to time.

Occasionally latent diabetes will become manifest during treatment of a patient with Addison's disease. Fortunately, adequate replacement therapy with adrenal steroids makes it possible to control the diabetes relatively easily by the usual measures of insulin and diet.

Very rarely a patient with Addison's disease may develop an acute cortisone psychosis at the onset of therapy, even with relatively small doses of hormone. We have observed one such case in a woman with chronic slowly progressive adrenal insufficiency who became depressed, negativistic, and paranoid after a single oral dose of 25 mg. of cortisone. She was then maintained on desoxycorticosterone alone, and, fortunately, after a few days her psychosis subsided and she was able to resume cortisone therapy in physiological doses without further difficulty. We have not observed psychoses in any patient once treatment has been established.

No evidence has yet appeared to suggest that the use of adrenal steroids in physiological amounts has in any way reduced resistance to infection or accelerated the spread of any infectious process in persons so treated. Rather the reverse is true: These patients have fewer infections after treatment, and no reports have come to our attention of a flare-up in tuberculosis following treatment in patients whose adrenal insufficiency was due to this disease.

By stimulating gastric secretion, ordinarily reduced in Addison's disease, cortisone therapy may be expected to increase the frequency of peptic ulcer in these patients. There is no reason to believe, however, that the incidence of ulcer will be any greater in the treated Addisonian than in the general population nor should ulcer management be any more difficult.

Conclusion

The advent of the synthetic glucocorticoids, cortisone and hydrocortisone, and more recently the mineralocorticoid fludrocortisone has provided complete oral replacement therapy for patients with Addison's disease. By the proper adjustment of dosage these patients can be restored to normal health and activity and may be expected to survive without harm all of the stresses of modern living which they are likely to encounter.

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Case Reports

PROLONGED SHOCK IN DISSECTING AORTIC ANEURYSM

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DISSECTING aneurysm of the aorta is a clinical entity which, at the present time, is being diagnosed during life with increasing frequency. No longer is this diagnosis the exclusive province of the pathologist at the postmortem table. Shennan,[1] in his comprehensive monograph on the subject, states somewhat ruefully that, "of 16 cases encountered post mortem, none were diagnosed during life." Clinical awareness of the possibility of this condition as a cause of catastrophic cardiovascular illness is now so widespread that a similar compilation today would undoubtedly show that the correct diagnosis had been made, or at least suspected, in a considerable percentage of the cases.

As long as there was no adequate treatment for this almost invariably fatal condition, correct diagnosis, though of course desirable, was somewhat academic. The remarkable progress of cardiovascular surgery in the past decade affords promise that some method of correcting or alleviating this largely mechanical defect may be found. Attempts have already been made in this direction. Shaw,[2] in a recent communication, reports on a correctly diagnosed case where a fenestration procedure was performed on the internal wall of the aneurysm. The rationale of this procedure is an attempt to produce surgically a double-barreled aorta. This is the mechanism by which recovery occurs spontaneously in the rare instances of the natural disease where the dissecting aneurysm ruptures back into the lumen of the aorta. Though the patient eventually died with kidney failure in uremia, the operation seems to have achieved the mechanical correction it attempted.

Another consideration is the importance of withholding measures which might further reduce the already slim chance of recovery. In most incorrectly diagnosed cases the patient is believed to have sustained a myocardial infarction, for which anticoagulant therapy is frequently administered. Such treatment would of course be contraindicated for a dissecting aortic aneurysm.

The diagnosis, even today, is not easily made in many instances. The signs and symptoms may vary greatly, as does the extent and speed of the dissection. Sudden onset of severe chest or abdominal pain is the chief characteristic. Usually the patient is a person who has previously shown no evidence of cardiovascular disease and is apparently in a relatively good state of health. In most cases a history of preceding hypertension is obtained. In differentiating dissecting aortic aneurysm from acute myocardial infarction, the condition with which it most likely to be confused, two factors are emphasized as being of great importance, the blood pressure and the electrocardiogram. Thus the statement is made that in the former the blood pressure is likely to remain elevated or even go higher whereas in the latter the pressure usually drops. Furthermore, though electrocardiographic changes may occur in dissecting aortic aneurysm they are usually of a nonspecific character.

The case of dissecting aneurysm of the thoracic aorta here reported is of interest because both of these criteria failed to indicate the correct diagnosis. The patient was admitted in shock without any blood pressure

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reading obtainable, and throughout her hospital stay this remained the presenting clinical finding towards which therapeutic measures were directed. Serial electrocardiograms showing changes, including those described in atrial infarction,[3] were also misleading. In most instances of dissecting thoracic aneurysm death is caused by rupture into the pericardial sac with resultant cardiac tamponade, and this case terminated in that manner.

Report of Case

A 65-year-old white woman was admitted to the medical service of Morrisania Hospital on Feb. 25, 1955, in a state of shock. A short time before being brought to the hospital by ambulance she had complained of a sudden severe chest and upper abdominal pain and had collapsed. She was a known hypertensive for many years, but there was no history of angina or cardiac failure. On examination she appeared in shock. She was very pale, and her skin was moist and cold. Her temperature was 99.2 F. No pulse or blood pressure reading could be obtained. The heart sounds were inaudible. Abdominal examination revealed no abnormality. There was no edema or other evidence of heart failure.

Treatment for shock was begun immediately. The patient was given an intravenous infusion of 5% dextrose in water to which was added 4 cc. levarterenol (Levophed) bitartrate (1 mg. [base] per cc.). A few minutes after the infusion was started she became unconscious, whereupon an

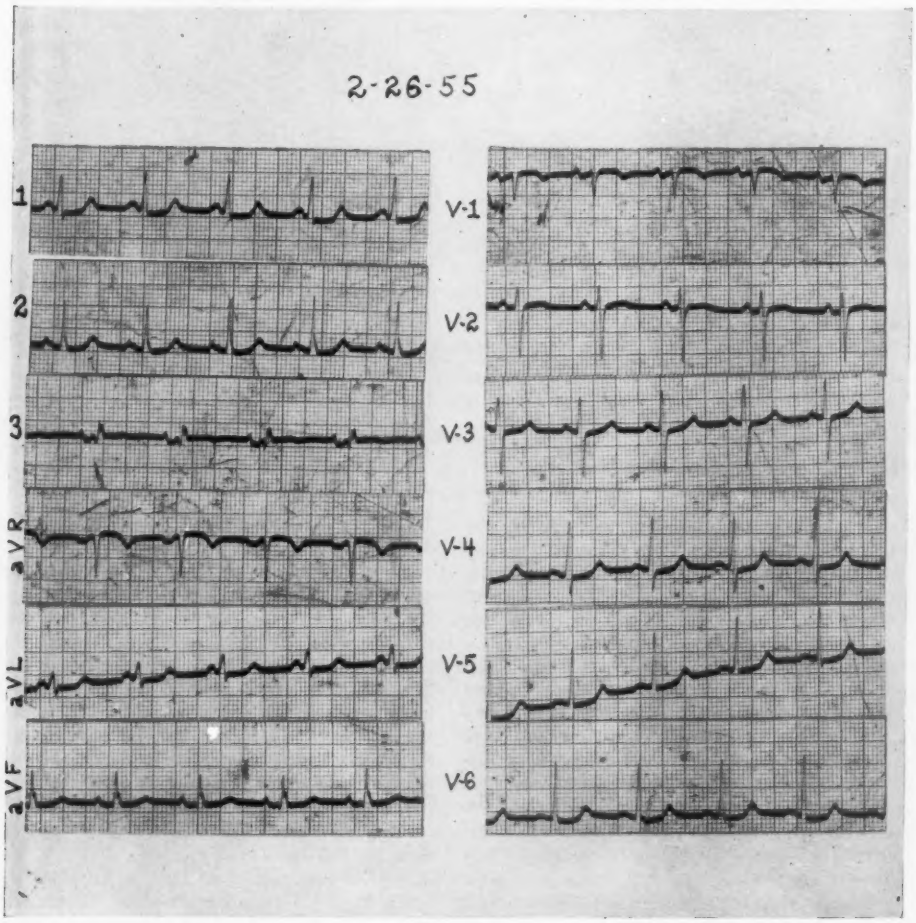

Figure 1

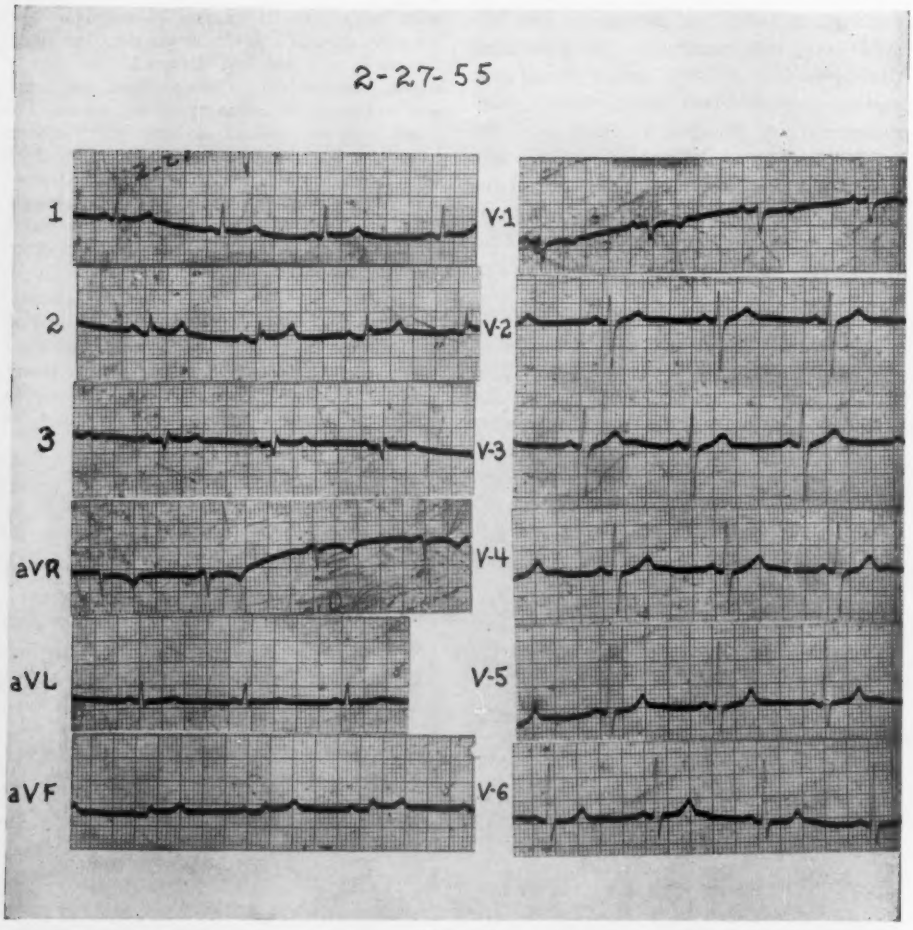

Figure 2

additional 4 cc. of levarterenol was added to the infusion bottle. She began to vomit, and shortly thereafter a feeble pulse could be felt for the first time. Within an hour a blood pressure reading of 100/60 was obtained. Thereafter the patient was maintained on continuous intravenous infusions and carefully observed. Whenever her blood pressure dropped or other signs of shock appeared levarterenol was added to the infusion bottle. Until her death, on March 9, she received a total of 68 cc. of arterenol. The maximum amount in any 24-hour period was on the second hospital day, when she received 16 cc. Subsequently, however, she was able to do without levarterenol for several 24-hour periods without any drop of blood pressure or signs of shock.

Urinary output was scanty for the first three days after admission; on the second day there was complete anuria. Thereafter the urinary output varied between 920 and 1480 cc. daily.

On Feb. 28, the third hospital day, the patient developed a left facial paralysis. She remained conscious, and her general condition appeared better. The paralysis disappeared the following day, leaving only a slight residual slurring of speech. Thereafter she continued to improve, not complaining of any pain and appearing fairly comfortable. During the early morning hours of March 9 she developed gasping respiration, her blood pressure became unobtainable, her pulse became weak and irregular, and she died within a few minutes.

Laboratory procedures revealed the following findings: Numerous urine specimens showed a specific gravity varying from 1.005 to 1.020 and albumin varying from a trace to 1+. Microscopic examination revealed only occasional white blood

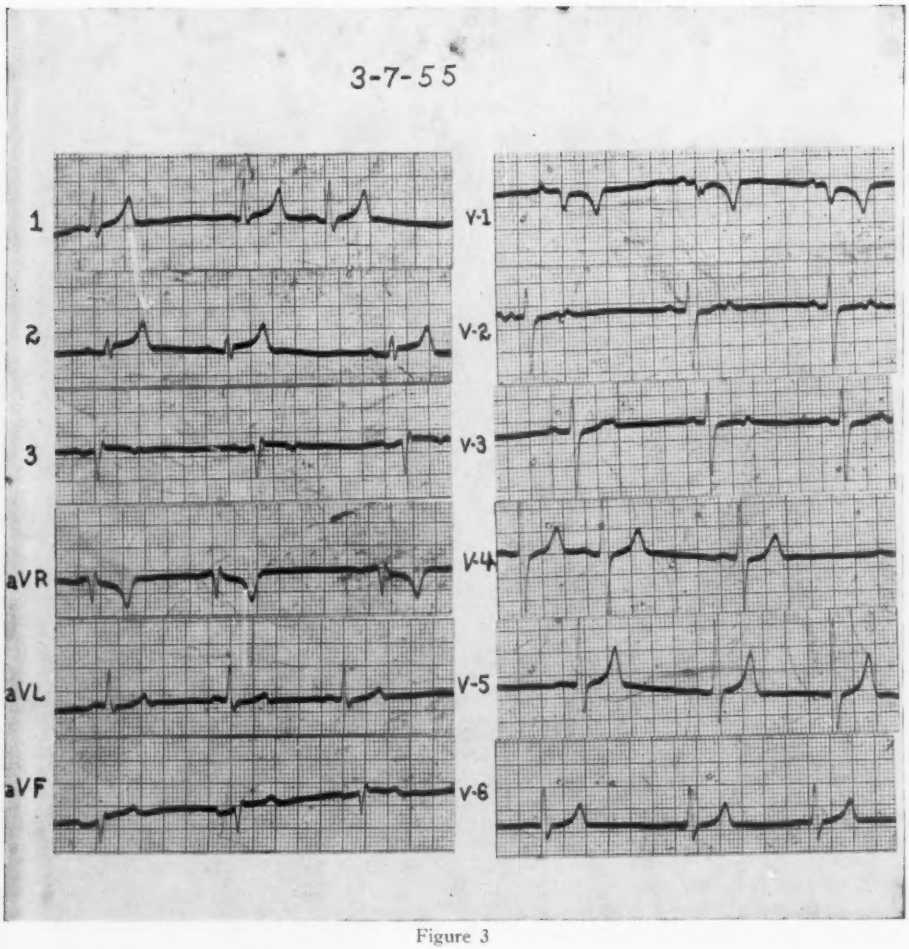

Figure 3

cells ranging to 10-20 per high-power field.

The blood showed a hemoglobin of 9.5 gm., with a hematocrit value of 32%. The white blood cell count was 8800, with 86% polymorphonuclear leucocytes and 14% lymphocytes. Blood chemistry values were as follows: Urea nitrogen, 102 mg.; creatinine, 7.5 mg.; glucose, 95 mg.; sodium, 126 mEq/L.; potassium, 6.0 mEq/L.; chlorides, 92 mEq/L.

Four electrocardiograms were taken, one soon after admission, the second the following day, and the third and fourth on the ninth and tenth hospital days. The first electrocardiogram showed a depressed ST interval in Leads I, II, aV_L, V_4, V_5, and V_6 and a depressed PQ interval with a distinct P-T_a wave in Lead III, the latter finding suggesting atrial infarction.* By the following day these findings were no longer present, but there was a slight shift of the electrical axis to the left, with a more prominent Q-3. The third electrocardiogram revealed more marked left axis shift, intraventricular block, and high peaked T waves. The last electrocardiogram showed, in addition, elevated ST intervals in Leads I, II, and aV_F and runs of ventricular tachycardia.

Postmortem Examination.—The heart weighed 650 gm. There was a moderate left ventricular hypertrophy. The pericardial cavity contained approximately 400 cc. of blood mixed with clots. There was a reactive pericarditis, with serofibrinous exudate present on both pericardial surfaces. There was moderate sclerosis of the aortic and mitral valves, especially at the free edges. The tricuspid and pulmonary valves appeared normal. The coronary ostia were patent, and the coronary arteries

* References 3 and 4.

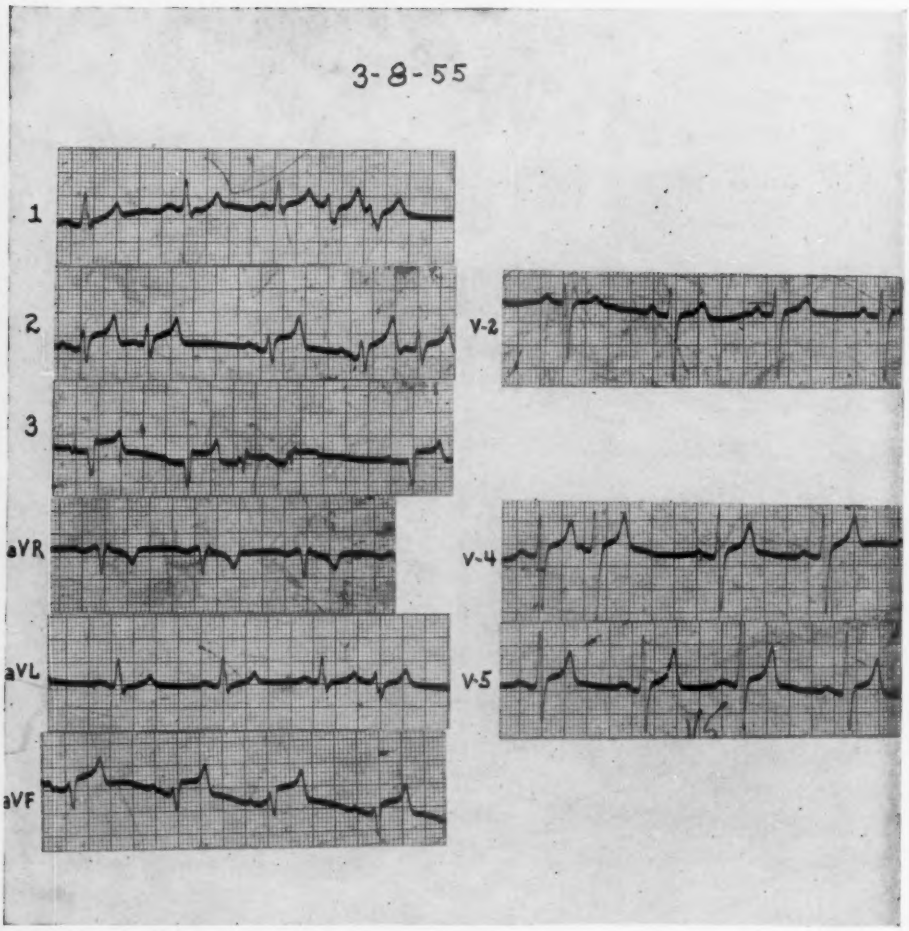

Figure 4

showed only slight atheromatosis. The aorta showed a dissecting aneurysm involving the arch, with formation of a sac about 6 cm. in diameter above the coronary ostia, and a large perforation into the pericardium. There was an organized blood clot overlying the site of rupture. The right auricle showed diffuse subendocardial hemorrhage. All branches of the aorta were patent. The right renal artery was unusually small in diameter, but there was no evidence of circulatory impairment of the right kidney.

The lungs were edematous, oozing a frothy serosanguineous fluid on pressure, but otherwise they showed no abnormality. The bronchial tree was clear. The liver weighed 1600 gm. and showed some congestive changes. The adrenals were normal. The kidneys weighed 130 gm. each. The capsules stripped easily, disclosing a finely granular surface. There were a few small cortical cysts containing serous fluid, and the cortex itself appeared narrow, but the kidney parenchyma otherwise appeared normal. The pelves were congested. Both ureters were normal.

The rest of the postmortem examination revealed no pertinent findings. The pathological diagnoses were the following: (1) ruptured dissecting aneurysm of the arch of the aorta, (2) hemopericardium with reactive pericarditis, (3) pulmonary edema, (4) moderate hypertrophy of left ventricle, and (5) minimal coronary sclerosis.

Comment

Prolonged hypotensive shock was the outstanding clinical manifestation in the case of ruptured aortic aneurysm herein de-

Fig. 5.—Postmortem specimen showing aneurysmal sac. Arrow points to site of initial rupture and dissection.

scribed. It persisted in varying degree throughout the patient's hospital stay and was successfully combatted by the use of intravenous infusions containing levarterenol, as described in the recent literature.[5] Death occurred when the aneurysm ruptured into the pericardial sac, producing cardiac tamponade. The autopsy findings of reactive pericarditis and the presence of organized blood clot overlying the rupture site would seem to indicate that seepage of blood into the pericardial cavity preceded this terminal event. The usual clinical picture described in this condition is one of maintained or even elevated blood pressure, and the importance of this finding in the differential diagnosis from myocardial infarction is emphasized.

This case further demonstrates that the electrocardiographic findings may also be misleading. While there were no changes typical of myocardial infarction, the rapidly changing pattern would be consistent with this diagnosis. The P wave changes seen in the first electrocardiogram, suggesting atrial infarction, may actually have been due to the diffuse subendocardial hemorrhage of the right atrium found after death. Electrolyte disturbances associated with azotemia, particularly hyperpotassemia, undoubtedly contributed to the changes seen in the last two electrocardiograms.

Summary

A case of prolonged hypotensive shock associated with a dissecting aneurysm of the aorta is described. The shock responded to therapy with levarterenol (Levophed) until death resulted from rupture of the aneurysm into the pericardial sac, with resultant cardiac tamponade. P wave changes described in atrial infarction were found in the electrocardiogram.

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EPIDEMIC HEMORRHAGIC FEVER APPEARING IN THE UNITED STATES

Report of a Case with Renal Biopsy Studies

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THE APPEARANCE of a "new" disease is a noteworthy event, whether it be the first appearance anywhere or whether it be the appearance for the first time in a new locale.

In 1951 the United Nations forces in Korea were subjected to an outbreak of a strange acute febrile illness characterized by prostration, abdominal pain, shock, and hemorrhagic manifestations. U. S. Army physicians finally identified this as identical with an illness studied about 15 years ago by the Russians and Japanese in Siberia and Manchuria, respectively.*

In December, 1953, a veteran of the Korean war was admitted to the V.A. Hospital, Brooklyn, suffering from an obscure, unusual infection that we now believe was epidemic hemorrhagic fever.

It is our purpose in reporting this case to call attention to the fact that epidemic hemorrhagic fever can and does appear in recent Korean veterans in the United States, to record certain observations in reference to the renal pathology during the convalescent phase, and to review the differential diagnoses of this disorder when it appears outside the epidemic area.

Report of Case

A 23-year-old, recently discharged, white male veteran was admitted to the Brooklyn Veterans Administration Hospital on Dec. 15, 1953. He had served with U. N. Armed Forces in Korea, having been in the Kumwha area from January, 1953, to Nov. 9, 1953. From Nov. 10 to Nov. 15 he was at the Port of Embarkation at Pusan, and from then until Nov. 30 he was homebound on a Navy transport vessel. Malarial suppressives were discontinued on arrival.

On Dec. 9, 1953, thirty days after having left Kumwha and six days prior to his admission to the hospital, he developed shaking chills which lasted for a few moments unaccompanied by any other symptoms. On the following day, he suffered several attacks of shaking chills now accompanied by intense subjective vertigo, generalized malaise, and anorexia. Four days before admission, because of the persistence of these symptoms, he consulted his physician, who noted his temperature to be 105 F. Over the course of the following four days and up to the time of admission, he was given a total of six quinine capsules and a daily injection of penicillin. This medication produced no apparent change in his clinical status. Three days prior to admission, he started to vomit several times daily, had about 20 diarrheal movements per day, and developed a hacking, nonproductive cough. In the 48 to 72 hours preceding admission, generalized muscular aching, diffuse abdominal pain, right flank pain, sore throat, and severe lassitude developed. He denied the presence of a rash or any urinary signs or symptoms.

Physical examination on admission revealed a well-developed well-nourished young white man who appeared lethargic and acutely ill. His temperature was 102.0 F; pulse rate, 112; respirations, 20, and blood pressure, 128/82. His responses to questions were slow and occasionally irrelevant. The facial skin was flushed and warm, and the conjunctivea were slightly reddened. Both tympanic membranes were somewhat injected. The pharynx was deeply and diffusely reddened and covered by a thick whitish exudate on the posterior wall. There was slight splinting of the right hemithorax. The heart was not enlarged to percussion. The abdomen was scaphoid and diffusely tender, without spasm, rigidity, or rebound. There were no abnormal masses or palpable organs. Examination of the back revealed marked spasm of the lumbodorsal muscles, more pronounced on the right, with severe punch tenderness in this area. Examination of the extremities revealed questionable cyanosis of the nail beds but no petechiae, clubbing, or edema. The submandibular and axillary lymph nodes were moderately enlarged and

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From the Medical Service, Veterans Administration Hospital, Brooklyn.

* References 1 and 2.

tender. Results of neurological examination were within normal limits.

Laboratory Data.—Hemogram at the time of admission revealed hemoglobin, 16.2 gm.; WBC, 11,700/cu. mm. neutrophiles, 70%; lymphocytes, 30%; ESR, 2 mm. in an hour. On the following day, hemoglobin was 14.1 gm.; WBC, 9200/cu. mm.; neutrophiles, 44%; lymphocytes, 52%; eosinophiles, 4%. Some of the lymphocytes appeared atypical but not characteristic of infectious mononucleosis. Admission urinalysis revealed specific gravity, 1.008; proteinuria, 2+; sugar, negative; reaction, acid, and occasional finely and coarsely granular casts per low-power field and 3 to 6 RBC per high-power field. Occasional WBC were also seen. Serologic test for syphilis and five examinations of the blood for malaria and for heterophile antibodies were negative, as were cold and Streptococcus MG agglutinations and antistreptolysin titer, on three occasions. Agglutination studies revealed typhoid H titer of 1:160 on Dec. 18, 1953, and of 1:80 ten days later. Blood urea nitrogen on Dec. 10, 1953, was 23.5 mg./100 cc.; Dec. 23, 1953, it had fallen to 9 mg./100cc., and it remained at this level throughout the remainder of patient's hospital stay. Fasting blood sugar was 89 mg./100 cc. Liver chemistry studies on admission revealed normal values except for 3+ cephalin flocculation. On Dec. 22, 1953, thymol turbidity was 12.2 units; cephalin flocculation, 4+, and sulfobromophthalein retention, 7.5%. On Feb. 9, 1954, liver chemistry values returned to normal.

Daily urinalyses were performed. During the first five days of the patient's hospitalization, the urine consistently showed 2 to 3+ proteinuria. However, after the first week there were only traces of protein found and after the second week the urine was completely free of protein. On Dec. 28, 1953, 24-hour urinary albumin excretion was 0.36 gm. For the first week the specific gravity of the urine was fixed at about 1.010. However, it gradually increased from this time. Fishberg concentration test on Dec. 29, 1953, revealed maximum concentration to be 1.017; on Jan. 1, 1954; the value was the same; Jan. 13, 1954, maximum concentration was 1.022, and by Jan. 19, 1954, it had risen to 1.025. At no time did the centrifuged sediment contain more than 3 to 6 RBC per high-power field, and after the first week the urine was free of red cells. A few finely and coarsely granular casts were present during the first week of hospitalization. Urea clearance on Dec. 30, 1953, was 35% of normal. Phenolsulfonphthalein (PSP) excretion on Dec. 30, 1953, was 6% in 15 minutes, 30% in 1 hour, and 41% in 2 hours. On Jan. 15, 1954, the PSP excretion values were as follows: 15 minutes, 25%; 1 hour total, 65%, and 73% in 2 hours. On Jan. 15, 1954, inulin clearance was 129 ml. per minute and *p*-aminohippuric acid clearance was 682 ml. per minute (not corrected for body surface area). These are within normal limits.

Agglutination studies for Leptospira ictohemor-

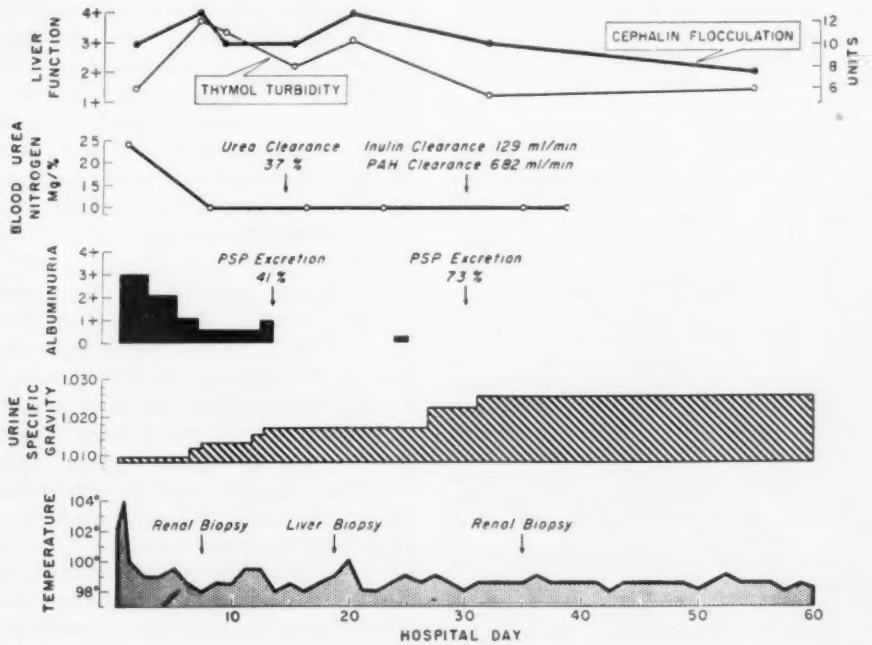

Figure 1

rhagiae, Leptospira pomona, and Leptospira canicola were negative in three widely separated † laboratories. Additional serological studies for strains of Leptospira which are found in Korea were performed by the Army Medical Service Graduate School Laboratories and were found to be negative. Trichinella and Amoeba complement-fixation tests were negative. Stool examinations were negative for ova and parasites. Throat culture revealed B. proteus predominating. The white cell count remained at normal levels, with the disappearance of the abnormal lymphocytes. Sedimentation rate rose to a maximum of 21 mm. in an hour after one week. Chest x-ray, ECG, and intravenous pyelogram were normal. Liver biopsy on Jan. 4, 1954, revealed normal liver. Renal biopsies were performed on Dec. 23, 1953, and on Jan. 20, 1954.

Hospital Course. (Fig. 1).—A few hours after admission the patient's temperature rose to 104 F, without chills. The abdominal and flank pains were of such severity as to require meperidine (Demerol). During the first 24 hours the patient vomited on two occasions and had three loose brown bowel movements. Treatment consisted of parenteral fluids and atropine for the gastrointestinal symptoms and acetylsalicylic acid. On the second hospital day the patient's temperature had fallen to normal, and it remained normal throughout the rest of his hospitalization. On this day it was noted that the throat had become considerably more reddened and a small mucosal hemorrhage appeared on the soft palate. For this reason, penicillin therapy was instituted, and this was maintained for a period of 10 days. After the first 24 hours of hospitalization clinical improvement was striking. The patient no longer appeared acutely ill and toxic; his sensorium had cleared, and he was alert. The abdominal and flank pains had diminished considerably and had practically disappeared by the third day. There was no recurrence of nausea, vomiting, or diarrhea, and his appetite improved rapidly. During the first three days cervical lymphadenopathy became more prominent and tender. After the fifth day the nodes were no longer tender; however, lymph node enlargement persisted for about two weeks. By the end of the first week the pharynx had returned to normal in appearance, and the patient was completely asymptomatic. The blood pressure remained at normal levels throughout the entire hospital stay. The quantity of urine was normal at all times (i.e., no oliguria or polyuria). The patient remained well throughout the remainder of his hospital stay and subsequently while being followed. Urinalyses on repeated follow-up visits have been normal, no albuminuria or formed elements being present, the specific gravity being maintained at high levels.

† Army Medical Service Graduate School Laboratories, Washington, D. C.; New York State Department of Health Laboratories, Albany, N. Y.; U.S.P.H.S. Communicable Disease Center, Chamblee, Ga.

Comment

In summary, a young veteran, recently returned from the Korean battleground, where epidemic hemorrhagic fever was occurring, was seen with the following clinical picture: fever, facial and conjunctival flushing, malaise and prostration, abdominal and flank pain, albuminuria with hyposthenuria, and a solitary small pharyngeal hemorrhage. The abdominal pain was an important feature of the early course and was very severe. There was no response to penicillin therapy.

In attempting to diagnose this disease, our thinking followed a course similar to that of most observers when they first encountered this and related infections. It was apparent that this was not a common upper respiratory infection with "febrile" albuminuria, since the redness of the face and eyes was much more intense and the degree of albuminuria with the low urinary specific gravity was incompatible with this. Acute hemorrhagic nephritis was considered to be unlikely because of the absence of formed elements, the hyposthenuria, and absence of significant azotemia, edema, and other typical findings. There was no exposure to known nephrotoxins and, while a sensitivity reaction to quinine was considered, this too was discarded as unlikely.

The clinical appearance of the patient suggested most of all either a rickettsial or a leptospiral disease, the latter seeming the more likely because of the nephropathy and disturbance of liver function. Serologic studies, however, eliminated these. Malarial parasites were not found despite diligent searching. This left us with a new febrile disease which injured the kidney much as does a "lower nephron nephrosis," with albuminuria and prolonged hyposthenuria and without such known causes as drugs, other chemicals, shock, severe prolonged hyperpyrexia, or alkalosis. We were brought to

consider epidemic nephropathy and epidemic hemorrhagic fever.

In 1934 Zetterholm [3] described a series of cases in Sweden thought to be acute nephritis with a clinical picture suggestive of acute abdominal catastrophe. Independently, Myhrman [4] described a series of cases of nephropathy with unusual symptoms. During the German occupation of Finland,[5] the German troops were subject to an epidemic of this disease, and extensive testing for Leptospira failed to isolate these organisms or to reveal the cause. Isolated small outbreaks have been reported from northern Scandinavia, especially among hunters and adventurers in the wilderness.[6]

Characteristically this disease resembles very mild hemorrhagic fever without hemorrhagic phenomena. The onset is acute, with fever up to 104 F; headache; vomiting, and generalized aches and pains of increasing intensity, especially in the abdomen and flanks, suggesting an acute surgical abdomen. This phase ends in several days and is replaced by an afebrile renal phase characterized by oliguria, azotemia, and proteinuria followed by a period of diuresis and prolonged hyposthenuria. While shock does not occur, the German account mentions mild hypotension in the early renal phase. Recovery is the rule.

Hemorrhagic fevers similar to epidemic hemorrhagic fever have been reported in great detail from various areas in the Soviet Union.[6] Some of these are virus infections whose agents have been isolated and found to be transmitted by insect vectors. Indeed, both Russian and Japanese investigators studying Far Eastern epidemic hemorrhagic fever isolated viruses, while American investigations of the United Nations epidemic failed to isolate the causative agent.

At any rate, whether or not these syndromes have a common cause, there is a basic clinical similarity which is distinctive. They all start with high fever and trunk pain lasting for several days and are followed by a renal phase. Oliguria and then diuresis occur, with slow restitution of renal function to normal. Liver-function tests are abnormal, although jaundice does not occur. Hemorrhagic phenomena, when they occur, appear during the oliguric phase. It should be noted that in the case we report, with the paucity of hemorrhagic findings, the mild syndrome resembled epidemic nephropathy more than epidemic hemorrhagic fever.

The diseases vary considerably in their severity. Scandinavian epidemic nephropathy is primarily a benign mild self-limited disease. Epidemic hemorrhagic fever, on the other hand, may vary from a mild disease, as in the present case, to a severe fulminant hemorrhagic disease with shock and early death. Between these extremes, the disease may present a variety of complicated phenomena involving fever, hemorrhages, shock, and large shifts of body fluid because of disseminated vascular injury and repair.

This is the second case to be reported in the United States.[7] The first one reported was apparently infected at the same time and place as our patient. However, this patient was more acutely smitten and his disease followed a more typical course, with oliguria, azotemia, leukemoid blood reaction, hyposthenuria, hemorrhages, and a diuretic phase.

Histologic Studies of the Kidney

Biopsy specimens were taken with a Vim Silverman needle, according to landmarks taken with the help of an intravenous pyelogram.

Biopsy specimens taken Dec. 23, 1953, (Figs. 2 and 3): The proximal convoluted tubules show markedly swollen cells, some of which show disruption of the cell membrane and projection of granular cytoplasm into the lumens. Some tubules, seemingly in the loop of Henle, have definite necrosis with no discernible nuclei. Some of these stain deeply basophilic and are positive for calcium. Many of the tubule lumens contain protein, some of which is granular and represents cellular detritus and slough cells. In other lumens this granular debris merges with contiguous necrotic cells. The glomeruli seem uninvolved, but protein is present in some Bowman's spaces. No interstitial infiltrate is noted, but some edema is present. No vascular lesions are noted in the tissue studied.

Biopsy specimen taken Jan. 20, 1954 (Figs. 4 and 5): These sections differ from the previous sections in that the degenerative changes in the

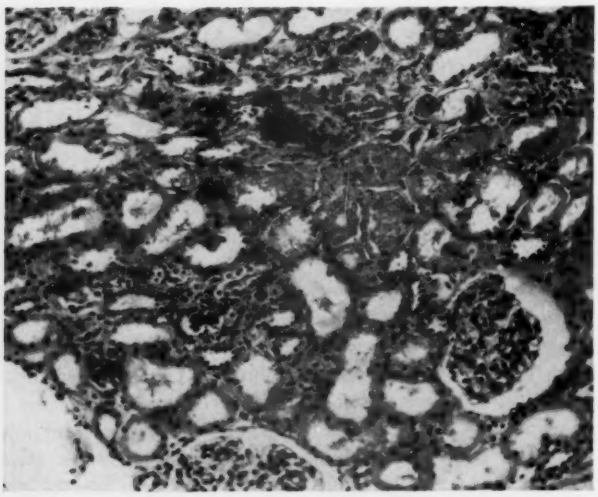

Fig. 2.—Swelling of cytoplasm and disruption of cell membranes in convoluted tubules; thin limb with cellular degeneration, sloughing, extrusion of cellular material into lumen; calcification; × 125.

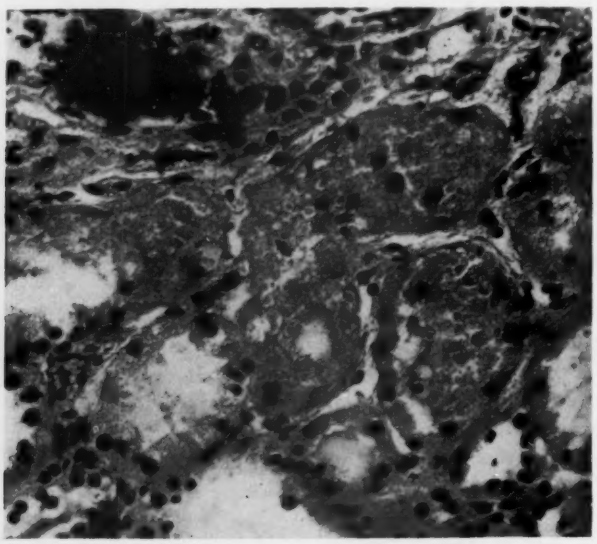

Fig. 3.—High-power detail of Figure 2; × 450.

convoluted tubules have diminished in intensity. Degenerative changes consisting of necrosis and calcification in the loop of Henle are still pronounced and demonstrate considerably greater calcific deposit than previously. These changes are interpreted as being those of resolution and healing.

Periodic acid-Schiff stains of both biopsy specimens demonstrated the basement membranes of glomeruli and tubules to be intact. The von Kossa stain was used to demonstrate calcium.

The lesions found in these biopsies are those of diffuse injury affecting the convoluted tubules and the loop. No apparent injury to the glomeruli or vessels was noted. This is compatible with the marked albuminuria which appears in toxic states affect-

ing primarily the tubules. The lesions appear to be primarily degenerative, and there is little inflammatory response in the injured areas. The second biopsy, taken about 41 days after the onset of the illness, still shows degeneration of proximal tubule cells with some sloughing of material into the lumen and necrosis of the loop epithelium. This occurred 1 month after defervescence, 20 days after the last clinical observation of albuminuria, and after *p*-aminophippuric acid and inulin clearances and PSP excretions were normal.

Lukes,[8] in his report on the renal path-

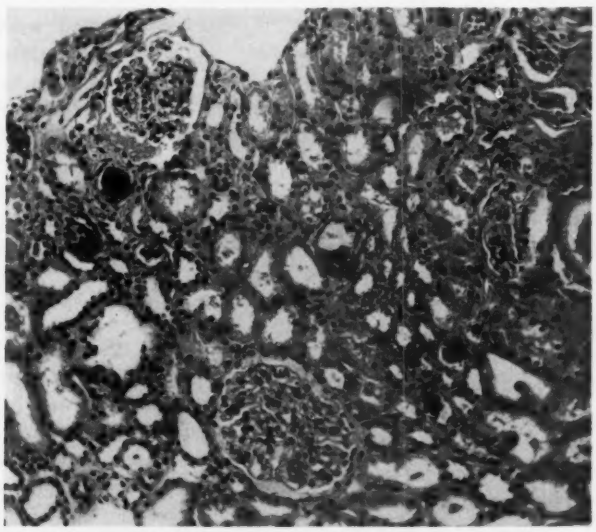

Fig. 4.—Regression of degenerative changes in convoluted tubules but increase in degree of calcification in loop of Henle; × 125.

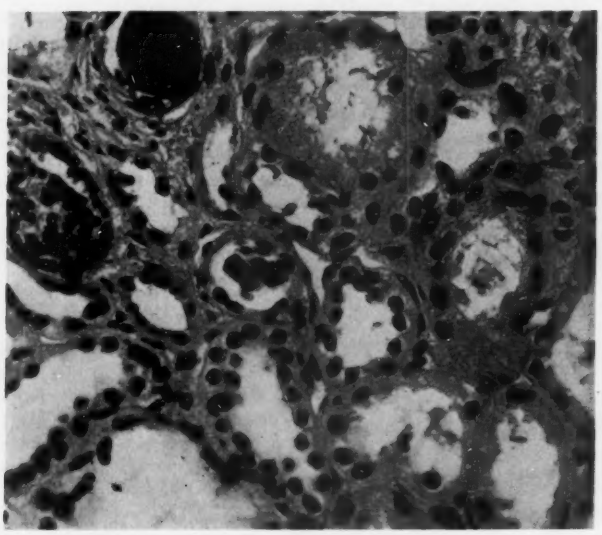

Fig. 5.—High-power detail of Figure 4; × 450.

ology of acute fatal hemorrhagic fever, describes intense congestion separating the tubules and foci of tubule epithelium necrosis which resembles "lower nephron nephrosis." Such necrosis occurred in 20% of his cases. Changes in the proximal convoluted tubules, similar to those observed by us, were seen. He noted further that during the diuretic phase of the disease the lumens were usually dilated and devoid of contents. In those cases in which death occurred after prolonged diuresis the epithelium was so flattened and hypocellular that it resembled an endothelial type of lining. Similar changes, most intense in the medulla, were found by Hullinghorst and Steer. While pigment casts have been observed by others, our biopsy specimens did not have any pigmented casts.

The information obtained from the renal biopsies was of help in confirming the clinical diagnosis. There are no truly pathognomonic changes in this disease, but when the changes are considered in conjunction with the clinical state the diagnosis is fortified. Further, the biopsies helped eliminate several conditions which were considered likely possibilities. The absence of glomerulitis was convincing evidence that this was not acute glomerulonephritis. The absence of focal interstitial nephritis was further reason for doubting that this was leptospirosis. Calcification of the renal tubules is very frequently found in mercury poisoning, but it occurs in the proximal portion of the nephron rather than in the loop. The patient was questioned in detail about exposure to nephrotoxic agents such as carbon tetrachloride, glycols, and mercury.

As observed in this patient, the lesions were those to be expected from a mild tubule poison. Histologically, the lesions resembled those nonspecific changes called variously "lower nephron nephrosis," "hemoglobinuric nephrosis," "necrotizing nephropathy," etc., which changes result from a multiplicity of causes such as shock, crush, transfusion reaction, drug intoxication, fever, dehydration, chemical intoxication, etc., all of which cause tubule damage primarily.

Pathologic reports of the state of the kidney in epidemic nephropathy are not available. However, one is tempted to guess on the basis of the clinical similarity that the histologic findings may be similar to those described.

The striking lesson learned from this study is that, even in this relatively mild case, the lesions are long in repairing, i.e., anatomic changes persist for a long period after clinical remission. No wonder the prolonged morbidity in the severer cases! On the other hand, one recovered patient who died from an unrelated cause three months after recovery had no histologic residua.‡ It appears from clinical data, also, that ultimately healing is complete.

Summary

A second case of epidemic hemorrhagic fever acquired in Korea but appearing in the United States is reported.

The case was mild and presented as a sore throat, severe abdominal pain, and influenza-like syndrome not responding to penicillin and marked albuminuria with hyposthenuria. Spontaneous recovery occurred.

The differential diagnosis is explored, and the resemblance to acute nephritis, leptospirosis, epidemic nephropathy, and toxic nephropathic states is discussed.

Renal biopsies were taken on two occasions during the period of observation, and the findings are considered in relation to the disease as we know it and in relation to differential diagnosis.

Dr. Joseph Smadel, of the Army Medical Service Graduate School, performed many of the serologic studies.

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Books

EDITED BY WILLLIAM B. BEAN, M.D.

BOOK REVIEWS

The Thyroid: A Fundamental and Clinical Text. Edited by Sidney C. Werner, M.D., Sc.D. (Med.), with sixty contributors. Price, $20.00. Pp. 789. Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 49 East 33rd St., New York 16, 1955.

About ten years ago the thiourea derivatives and radioiodine became available to medicine for experiment and therapy. Since then, the number of published investigations on the physiology of the thyroid gland and the therapy of its diseases has increased to such an extent that well over 3000 papers are said to be appearing annually in the medical literature. As a result of these studies, for example, the therapy of thyrotoxicosis has undergone two radical revisions in this decade. The newer tests of thyroid function and the current therapy of thyroid disease demand of the physician a detailed knowledge of the recent advances. The present book seems to be a logical means of furnishing him with this equipment. Sixty persons, each of whom has intensively cultivated a part of this field of knowledge, have contributed essays on the details most familiar to them. In this way the vast literature has been assimilated, evaluated, and presented authoritatively. The editor has done a superb job in organizing these contributions so that there is surprisingly little overlapping or verbosity. Eleven chapters are devoted to the physiology and biochemistry of the normal thyroid gland. The laboratory methods are fully dealt with in seven chapters. The embryology and anatomy are adequately covered. The clinical aspects of thyroid disease require twenty-three chapters.

I tried hard to find omissions in the coverage of the clinical discussions of the subject, but failed. Most of the obscure or rare items are adequately considered. Particularly effective is the presentation of different views of etiology and treatment by different authors sequentially, so that each theory is presented by a protagonist. The signs and symptoms of the diseases are described in detail, with indication as to the incidence, the mean laboratory values, and their ranges. Admittedly, this is the modern conventional method of presentation of clinical descriptions of disease. But the experience of teachers of medicine ever since Osler's day has shown that clinical symptoms and signs are better understood and remembered when encountered in the framework of case presentations. In a book of this size on a specialized subject the reader might hope to find detailed illustrative case protocols to supplement the brief descriptions now compressed into our crowded texts on general medicine and surgery. Where else would one look? The physician would like to be confronted with records of individual patients with thyrotoxicosis, the results of the thyroid-function tests, the doses of radioiodine given to each, the reasoning behind the decisions, the results of successive tests at intervals after therapy, how the patients changed at those times, and when the patients fully recovered. This method of presentation seems to place in perspective the signs and symptoms which are otherwise merely words to be remembered. For another example, it is correct and complete to state that patients with myxedema move and speak slowly. However, it has more meaning when I describe my patient who complained that as a radio performer she had found that she could only read 13 pages of material in 25 minutes, whereas formerly she could cover 20 pages in the same time. She had received much fan mail because of her slow and deliberate diction and was much chagrinned when she learned it was caused by myxedema.

The typography and layout of the book are excellent. The type face is pleasing and easy to read. The illustrations are few, but meaningful. The publisher should be censured for using highly glossed, heavy paper which is hard on the eyes and hard on the wrists (the book weighs nearly four pounds).

This book will be found a necessity for every hospital library, for every internist or surgeon who deals with thyroid disease. It is rather too detailed for the medical student.

ELMER L. DEGOWIN, M.D.

The Interpretation of the Unipolar Electrocardiogram. By Gordon B. Myers, M.D. Price, $4.75. Pp. 164, with 25 illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1956.

This small book will be enthusiastically received by the many physicians familiar with the author's splendid course in electrocardiography at Wayne University College of Medicine. The present book, the outgrowth of the supplemental manual to this course, was until now available only to the registrants.

It is a superior presentation, stripped of all the mystery surrounding the subject, and it clearly and authoritatively presents all of the necessary basic facts germane to the proper understanding, interpretation, and ultilization of the properly taken electrocardiogram. The author, one of the chief exponents of the Wilson concepts, is widely acclaimed for his painstaking electrocardiographic-pathologic correlations in myocardial infarction and ventricular hypertrophy. This information, formerly available only in the journal literature, is now collected. A special word should be said for the excellence of the discussion of the electrocardiographic changes attributable to right ventricular hypertrophy and to incomplete right bundle branch block. Much of the confusion is stripped from the uncertainties surrounding the rR', rSR', rSr', R, and qR complexes in right precordial leads. Even the arrhythmias are dealt with in surprisingly complete fashion for a book of this size.

The author, known to believe that the electrocardiographer should first of all be a physician, has written a textbook which will be equally useful to the medical student, general doctor, internist, and cardiologist. There are many who will use it so much they will wish it had been published with orthodox binding and printing rather than with offset lithography. However, in its present form the book is available at an attractive low price.

L. E. JANUARY, M.D.

The Treatment of Renal Failure. By John P. Merrill, M.D. Price, $6.75. Pp. 238, with 31 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1955.

This volume is an extremely valuable collection of data and ideas concerning the management of acute and chronic renal failure. The author is internationally known for his interest in renal disease, particularly for his work in homotransplantation of kidney tissue and use of the artificial kidney.

The book is a small one and suffers at times because certain subjects are treated with great brevity, but generally the concision is a virtue. It is easy to read despite, at times, a tendency toward the intemperate use of the adjective "marked." It is well edited (only two minor errors being found), but contains only the commercial name for some of the drugs mentioned.

The author's discussion of the treatment of renal failure by extrarenal routes and his discourse on the general topic of acute renal failure leave little to be desired. From the standpoint of clarity and excellence, these sections must rank with the best discourses on these topics in the English literature. One might quibble with some of the ideas expressed in the section on chronic renal failure, particularly as to the reasons for the use of testosterone and the blanket condemnation of sodium restriction in the treatment of this syndrome, but this section also approaches the others in quality. The three chapters entitled, "Normal Renal Function," "Normal Composition of Body Fluids," and "The Diseased Kidney" are outstanding for their lucidity and brevity.

This book should be a very useful one to medical students and to physicians who deal with renal failure in any form. It cannot be praised too highly, for it presents important, timely, authoritative material in a readable fashion. Internists especially will find this book a valuable one for information and frequent reference.

WALTER M. KIRKENDALL, M.D.

Differentialdiagnose innerer Krankheiten. By Dr. Robert Hegglin. $16.55. Pp. 678, with 372 illustrations. Georg Thieme, Herdweg 63, (14a) Stuttgart, 1956.

"Differential Diagnosis in Internal Medicine," by Dr. R. Hegglin, sees its aim in the selection and organization of medical knowledge for the practical purpose of bedside diagnosis.

Scientific completeness is not its object, since it cannot be realized by the physician in the sick-room.

The elements of the various branches of internal medicine, which are of importance in the diagnostic endeavors of the physician, are selected and presented in such a systematic manner that they can be utilized easily for the clinical problem at hand.

The general plan of the book is to start with the dominating symptom and, by integrations of additional manifestations and pathophysiological considerations, to arrive at the disease entity.

Reflections on the comparative "values" of symptoms and on the elements of the diagnostic process make for interesting and stimulating reading and show the philosophical inclinations and orientation of the European schools.

A search for order and unity and a need for reflection seem sometimes to exceed interest in detailed pathophysiological knowledge.

The great majority of the chapters deal, however, with specific clinical problems: dyspnea, edema, cyanosis, status febrilis, diarrhea, pain, and anemia are typical for the general arrangement of the text.

The book is beautifully printed and illustrated, conforming to the usual high typographical standards of the publishing house.

The clearness and preciseness of presentation and the lucidity of style, together with the typographical qualities, may account for the unusual success of the book. Since its first publication, in 1952, it has had one Spanish, two Italian, and four German editions.

HELMUT MUELLER, M.D.

How To Reduce Surely and Safely. By Herbert Pollack, M.D., with Arthur D. Morse. Price, $2.95. Pp. 157, with many charts, recipes, etc. McGraw-Hill Book Company, Inc., 330 W. 42nd St., New York 36, 1955.

Obesity is the number one form of malnutrition in contemporary America. In this book, Dr. Pollack describes in a clear and simple manner what is needed to reduce. The book is intended for laymen. The details of reducing diets are set forth with admirable clarity, and it should help physicians help patients. The unfortunate thing is many who should read it will not read it, many who read it will not follow it, some who follow it for a time will relapse, but for a select few it may help point the way to successful weight loss and then holding the line.

WILLIAM B. BEAN, M.D.

Sexual Precocity. By Hugh Jolly, M.D., M.R.C.P. Price, $6.75. Pp. 276, with many illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1955.

This interesting book is an account of the author's personal experience in the field, comprising 69 cases, preceded by a classification and discussion of sexual precocity and review of the literature. The author sets the upper limit of precocity at 10 years, for both boys and girls.

The first 96 pages of the book are devoted to a discussion of the various types of sexual precocity. These are classified as (1) cerebral, the commonest type (43 cases), which includes constitutional precocious puberty; (2) adrenal (9 cases); (3) gonadal (3 cases), and (4) miscellaneous (14 cases). Each type is discussed thoroughly as to pathogenesis, symptoms, treatment, and prognosis. The differential diagnosis between the various types is covered. This section is followed by a complete bibliography on the subject.

The last 151 pages are devoted to a documentation of the 69 cases the author has seen. The cases are well-described and documented and include pertinent history, physical findings, x-rays, and laboratory data. Many photographs are included in this section.

This is an invaluable reference work and will undoubtedly be in the library of anyone interested in sexual precocity.

JOHN M. REICHERT, M.D.

The Complete Medical Guide. By Benjamin F. Miller, M.D. Price, $4.95. Pp. 913, with more than 150 illustrations. Simon and Schuster, 630 Fifth Ave., New York 20, 1956.

There is no satisfying the great thirst of the layman for medical information and medical action. To this end we have much of the energy of the Boy Scout movement directed at first aid, courses on hygiene and health in grammar schools, a great host of medical articles written for the laymen in popular lay journals, and a vast and growing collection of medical books by physicians addressed to the laymen. Any medical book which declares itself complete is sure to be out of date before it has gone to press. Though this is true of a book for laymen, it is not so important, for probably there will be no new medical information based on any current discovery which the laymen should have to save his life.

While Benjamin Miller's new book doesn't have all the answers, it has a great many of them. It will be a great comfort to have in the house for consultation prior to taking action. Its five sections give a wealth of medical detail. The words, though not altogether simple, are much clarified by an extensive medical glossary. The divisions are as follows: You and Your Body; You and Your Mind; You and Your Home, You and Your Doctor; You and Your

Special Problems. The book gives a good balanced account. It avoids sensationalism. Designed to temper rather than foment fears, it still may arouse some, because many medical problems, not being simple, cannot be simplified. There is good sound instruction which should encourage our do-it-yourself nation to realize how often they are out beyond their depth and to call the family doctor.

It seemed worth while in reviewing Benjamin Miller's new book entitled "The Complete Medical Guide" to compare it with other books of home remedies, treatment, medical advice, and the like, and to this end I would like to make a comparison of it with "Domestic Medicine: or, a Treatise on the Prevention and Cure of Diseases, by Regimen and Simple Medicine; with an Appendix, containing a Dispensatory for use of Private Practitioners"—all this by William Buchan, M.D., F.R.C.P., Edinburgh, adapted to the climate and diseases of America by Isaac Cathrow, published in Philadelphia in 1797 and printed by William Folwell. According to the advertisement in the beginning, "Domestic Medicine" was not meant to replace the physician but to supply his place where medical assistance could not easily be obtained or until the doctor, sometimes fetched from afar, arrived. My copy happens to be one which belonged to John Holmes, one of my great grandfathers, trained by the physicians of the Dublin school of the 1820's and 1830's. He practiced briefly in Philadelphia before marrying a woman of some wealth and retiring from practice. Perhaps "Domestic Medicine" was used by his wife when she could get no help from her husband. The book has altogether 57 chapters and 476 pages, including 40 pages of how to concoct remedies. It is printed with the old S's looking very much like F's, so that on first reading I am not always sure what the man is "faying." Part I deals with the general causes of diseases, beginning with a chapter on children, then on laborious and sedentary occupations, then chapters on food, air, exercise, clothing, sleep, temperance, cleanliness, infection, the passions including religious melancholy, the common evacuations, and the effects of atmosphere and environmental hazards. Part II, on diseases, begins with a chapter on the general nature of fevers, on intermittent fevers and continual fevers, pleurisy, inflammation of the lungs, consumptions, and from there on more than 100 pages deal with all the puzzling concourse of fevers which were so vexing at the time and still may trouble us. Then we come to organ pathology, with diabetes and diseases of the kidney, hemorrhages, and dysentery. There is a chapter on jaundice wedged in between one on worms and one on dropsy. Then we run through rheumatism, scurvy, gout, asthma, apoplexy, costiveness, nervousness, diseases of the eye, cancer, poisons, venereal disease, diseased women, diseased children, surgery, dislocations, strains, ruptures, broken bones, and diseases caused by heat and cold. It might be worth comparing a couple of points taken at random. For instance, Buchan's book has this to say about heartburn. "It is not a disease of that organ but an uneasy sensation of heat or acrimony about the pit of the stomach which is sometimes attended with anxiety, nausea or vomiting. It may proceed from debility of the stomach, indigestion, bile, the abounding of an acid in the stomach and so on. People liable to this complaint ought to avoid stale liquors, acids, windy or greasy elements and they should never use violent exercise soon after a plentiful meal. The patient ought to take a dose or two of rhubarb. Afterwards he may use infusions of bark or any other stomachic bitters in wine or brandy. Exercise in the open air will be of use, and everything that promotes digestion—if wind causes this complaint, the most proper medicines are carminitives. I have frequently known the heartburn cured particularly in pregnant women by chewing green tea." Miller has this to say about "heartburn" or indigestion. "Heartburn has nothing to do with your heart. It is caused by your intestines. Omitting the gas forming foods such as cucumber or cabbage . . . often helps . . .. Heartburn can sometimes be *prevented* by taking a tablespoon of cream one-half hour *before* a meal. You may find relief after taking a level teaspoonfull of magnesia. It works far better than bicarbonate of soda."

As for the headache, Buchan very wisely avoids talking about the cause but he describes the different kinds and recommends safe but nonspecific moves. As for instance, "when the head-ach is occasioned by the stoppage of a running at the nose, the patient should frequently smell to a bottle of volatile salts. In hemicrania (migraine), gentle vomits must be administered as also purges of Glauber salts or jalap." He also recommends opiates for extremely severe headaches. General hygienic measures of diet, rest, etc., were described. In Miller's book headaches are discussed as a symptom, as migraine headaches, as tension headaches, as well as those connected with sinusitis, hayfever, and allergies. The circumstances when the headache is likely to be significant and when a doctor should be consulted are clearly stressed. The problem of migraine and tension headaches is set down well.

In the matter of sex, Doctor Buchan seems to confine most of his efforts to a discussion of

the well-known venereal diseases, whereas Miller talks a good deal more freely, and in fact chattily, about many things, including positions in intercourse, infidelity, and a good many cognate aspects of psychosomatic medicine and Freudian psychiatry. What Buchan says about love, however, should be respected. "There is no passion with which people is so ready to tamper as love although none is more dangerous." Of course, what Buchan doesn't have—hormones, vitamins, antibiotics, Freud, electrolytes, stress, what to do when the atomic bomb hits—he managed to do well enough without.

In any book as big as the "Complete Medical Guide" one finds faults and errors if he looks closely; but there are in fact very few in this book. For instance, on page 272 is the suggestion of treatment of the insanity of pellagra with vitamin B_2, which, though an outmoded term, usually means riboflavin, whereas nicotinic acid obviously is needed. On page 800 is a rather quaint notion that under certain circumstances natural foods might actually be substituted for multivitamin tablets. Having gone to the trouble of mentioning Doctor Lind and scurvy, Miller might have used his actual name, James rather than Joseph. But these are picayune comments.

I find both of these books absolutely fascinating reading. Miller's I would recommend as a book to be safe enough to be in the hand of most patients and certainly very useful to have about the home when wife or children are so persistent in their questions that patience runs low. While we think in terms of recent advances and great discoveries, it is chastening to see how little our fundamental knowledge has increased. So many of the problems which harry suffering humanity, from the common colds to boils, from headaches to cancer, are much the same and treatment often little better. This is not to say we have made no great advances. In fact these advances have been very thoughtfully incorporated into a book not only suitable for the layman but an important book to have available for handy reference and consultation. It is the kind that might well grace the physician's own shelves, since we have now come to the point where many physicians concentrating in a narrow field of specialization are in actual fact laymen when facing the vast majority of the ills and ails of the human body and of society at large. After referring to it a good many times in a few weeks, our family has not found any topic where it is impossible to get information even if the information was that we had better consult a physician.

WILLIAM B. BEAN, M.D.

Tuberculosis in the Army of the United States in World War II. By Esmond R. Long, and Seymour Jablon. Price, $1.50. Pp. 88, with 56 tables and 15 charts. Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., 1955.

The Greeks who were fond of philosophical disputations used to argue about how many stones make a heap. One is not a heap, nor two or three; five or six certainly are a heap. Where is the border line? So too it is implicit in any series which runs from a definite positive at one end to a definite negative at the other that there must be a point of transition somewhere in the series in which there is certain to be an error in evaluation of 50%. This is simple mathematics and applies to the reading of x-ray films of the chest in the appraisal of tuberculous lesions as well as to anything else.

The first part of this document is related to the evaluation of tuberculosis in soldiers, especially with reference to x-ray diagnosis of early lesions. The writers scratch their heads and worry about different observers differing in interpretation of borderline lesions or indeed about the same observer giving a different verdict on a second later reading, despite the fact that, as pointed out, a large error is mathematically certain. However, this heavily documented material is at least thorough, as are the statistics on tuberculosis in the army in World War II presented in the second part of the book. Every phase of the subject is analyzed, in too much detail to be reviewed here, but the array of facts should be invaluable to those especially interested.

ARTHUR L. BLOOMFIELD, M.D.

A Follow-Up Study of World War II Prisoners of War. By Bernard M. Cohen, Ph.D., and Maurice Z. Cooper, M.D. Price, $1.50. Pp. 81, with 43 tables and 5 figures. Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., 1954.

This small monograph, one of a series to be published by the Veterans Administration (or already in print; no series number or other means of judging is given) contains the data and conclusions from a record and questionnaire survey of nearly 8000 World War II prisoners.

The investigation was conducted jointly by the National Research Council and the Veterans Administration.

Three principal reasons for undertaking such a survey come to mind: (1) to gain experience in and evaluate the methods used, (2) to learn the answer to the question posed, and (3) to pick up unusual or chance observations which may give a clue to some apparently unrelated problem ("serendipidy"). The last often turns out to be the most profitable but is best left for the individual reader to discover.

The question posed was, for men taken prisoner during World War II, "to what extent their prison experience has affected their survival, their health, and their adjustment to civilian life." The data were taken from records, including those of death, hospitalization, and disability, and from questionnaires sent to survivors, and they cover a period of eight years after liberation. The analysis was done separately for prisoners from the European and Pacific Theatres, and the results were compared with a comparable control group of combattants who had not been imprisoned. In most categories those from Pacific prisons fared far worse than those from European internment. In fact, the latter in most categories were little different from the controls. The prisoners of the Japanese war are referred to as PWJ. (The book abounds in such alphabetical abbreviations, explanations for a few of which could not be found.) A few of the more important findings are mentioned herewith.

In the first place, the PWJ group experienced a far greater mortality than expected, than their European fellows or than the controls. It would not surprise anyone to find that tuberculosis was the largest cause of death. Accidents were a fairly close second, a somewhat unsuspected finding. Alcohol ingestion and psychiatric disturbances may have conditioned some of the accidents, but further than this no special study was made. Unfortunately, of all the deaths (83) autopsy records were found in the Armed Forces Institute of Pathology for only 9.

The morbidity of the PWJ was also in excess of the other two groups. All varieties of illness were reported. Beriberi and helminth infestation were the most frequently encountered, but other conditions not as directly related to the imprisonment were increased—e.g., benign and malignant neoplasms, various kinds of cardiovascular disease, and most other categories.

Many further data concerning health, work, and the like are included. Sufficient tabular material to assess the conclusions are presented. An index closes the work.

CHARLES S. DAVIDSON, M.D.

Diseases of the Chest. By H. Corwin Hinshaw, M.D., Ph.D., and L. Henry Garland, M.B., B.Ch. Price, $15.00. Pp. 727, with 277 figures. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

This well-organized and comprehensive one-volume text is extraordinary with respect to the thorough and all-inclusive coverage of the subject of diseases of the chest. Of forty chapters, two are devoted to the clinical history and physical examination, one to diagnostic laboratory studies, and one to the general subject of radiologic examination of the thorax. The segmental anatomy of the tracheobronchial tree and lungs is presented in some detail and with excellent illustrations; this chapter is a most valuable portion of the book. A concise discussion of pulmonary function studies not only includes those tests which are useful for clinical evaluation but also presents the basic concepts of normal and pathological physiology. This chapter will be readily comprehensible to the physician who is not specifically trained in pulmonary physiology; imposing mathematical formulae are not encountered.

The remaining chapters of the book are devoted to the various diseases of the thoracic structures, encompassing inflammatory, allergic, developmental, traumatic, degenerative, neoplastic, and vascular disorders. A wealth of information is presented in a most concise, readable, and informative manner. The illustrations (mostly roentgenograms) are numerous and well selected and have been reproduced with excellent clarity. The illustrations add immeasurably to the value of the book. Advances in therapy are adequately covered. The authors list only a small number of selected references. However, they state that many of these papers include extensive bibliographies.

This text has in every sense kept pace with recent developments in the field of chest diseases, both diagnostic and therapeutic. It will be a valuable reference for both the general practitioner and the internist.

E. O. THEILEN, M.D.

The Relief of Symptoms. By Dr. Walter Modell, M.D., F.A.C.T. Price, $8.00. Pp. 450. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1955.

Dr. Walter Modell has skillfully presented an intelligent and practical approach to the tedious matter of symptom therapy in the first portion of this three-part work: In this first part he discusses the frequent necessity and advisability of intelligently treating symptoms often even in the absence of a definitive diagnosis. He sites many pros and cons in the philosophy of treatment and in general advocates less compulsive diagnostic prerequisites to therapy. This approach is further augmented by emphasis on the importance of the ever present placebo effects, both positive and negative: Thus, some of the usual textbook type of dogmatism is avoided, resulting in a more practical approach to therapy. An understanding and proper use of these concepts presented in part one of this book, especially those dealing with the placebo action of drugs, will save time and worry and often needless calls for the general practitioner and specialist alike.

Dr. Modell suggests that the physician thoroughly believe in the patient's complaints, and he tells how the physician may relieve these distressing symptoms while at the same time the search is made for the basic causes of the disorder. If this attitude is followed wisely much quicker and better care results without danger to the patient.

The second part of the book is a section on therapeutic "pearls," specifically and concisely describing many common uses of drugs and therapeutic tools and other uncommonly emphasized drug actions. Each of 24 symptoms that bring 90% of the patients to medical aid are discussed separately as to the latest therapeutic agent or technique. The symptoms discussed are pain, anxiety, insomnia, gas, constipation, diarrhea, loss of appetite, obesity, palpitations, edema, dyspnea, cough, fever, weakness and fatigue, nausea and vomiting, vertigo, itch, hiccups, unconsciousness, convulsions, skeletal muscle spasms, menstrual disorders, frequency and dysuria, and jaundice. There is also a wealth of information on analgesics, sedatives, muscle relaxants, anticonvulsants, adrenergic drugs, anticholinergic drugs, digitalis materials, diuretics, chlorpromazine (Thorazine), and cortisone. The third part of the book gives excellent counsel with regard to cortisone and the masking of symptoms.

The book is recommended to all who are interested in the fine points of patient care as well as in diagnosis and specific disease therapy.

R. S. NORMAN, M.D.

Practitioners' Conferences, Held at the New York Hospital-Cornell Medical Center. Vol. 3. Edited by Claude E. Forkner, M.D., F.A.C.P. Price, not given. Pp. 293, with 10 illustrations. Appleton-Century-Crofts, Inc., 35 W. 32d St., New York 1, 1956.

The student "must see the master in action" said Billroth, than whom there was no greater clinical teacher, and Osler later insisted on having the students in the ward at the bedside. Curiously enough, modern teaching has drifted away from this fundamental principle; now there is usually a rigid and formal presentation of the patient's case, whereupon teacher and students leave the ward and the instructor gives a talk which could take place just as well in the amphitheater. At the same time that this absurd declension from the elementary principles of teaching medicine is going on, violent efforts are made on all sides artificially to "make things more graphic for the student"—hence audiovisual aids, television, groups, and panels. The Practitioners' Conferences in present book, says the preface, "have as their intent bedside teaching." To think that such a Barmecide feast could possibly replace bedside teaching surely declares the state of decay into which medical education is falling.

Take for example the following (p. 109):

"Dr. Kesten: I am afraid I am stressing, as Dr. deGara said, food too much. This patient is still sensitive to a few foods, wool, dust, and to bacterial allergens. We have not dealt much with the psychosomatic element which is very important in this patient.

"Chairman Forkner: Dr. Kesten, in each patient there has been mention that their conditions were aggravated by emotional factors. How important is that?

"Dr. Kesten: Dr. Cormia has written on that. He is far better able to judge than I.

"Dr. Cormia: Dr. Kesten is very modest.

"Dr. Kesten: I am talking too much.

"Chairman Korkner: Dr. Cormia, what would you say about it?"

Now, while no doubt this makes a vivid impression on those actually seated in the amphitheater during the conference, putting such material into print certainly serves merely to becloud rather than clarify the real issues.

A variety of subjects are discussed, the chairman leading and directing the questioning at his panels of experts; cancer of the skin, Hodgkin's disease, ulcerative colitis, tumor of the brain, and the common cold are a few of the topics taken up.

It would be charitable to say that these conferences as printed are of equal merit with a careful well-thought-out textbook article. Indeed, to me the best parts of them are the paragraphs in which one of the panelists gives a systematic discussion. The excellent summaries at the end of each section and the selected bibliographies are a feature of the book.

ARTHUR L. BLOOMFIELD, M.D.

Textbook of Endocrinology. By Robert H. Williams, M.D., and nine co-authors. Second edition. Price, $13.00. Pp. 776, with 175 illustrations. W. B. Saunders Company, 218 Washington Sq., Philadelphia 5, 1955.

It is seldom that a textbook attains completeness, accuracy, and clinical usefulness in the coverage of a broad clinical field to the extent that is accomplished in this volume. This second edition of Williams' popular text has had to be so radically revised in the light of the voluminous literature on the endocrines of the past five years that the chapters on the adrenals, ovaries, pancreas, thyroid, neuroendocrinology, and obesity have been completely rewritten.

Only an endocrinologist of Williams' stature could collect such a galaxy of stars to help in his enterprise of separating the wheat from the chaff in this vast and controversial field. This they have done with gratifying results. Each section contains an account of the anatomy and physiology of the organs under consideration and descriptions of the disease states due to hypofunction and hyperfunction, inflammation, tumors, etc., with a much more than cursory evaluation of diagnostic procedures and of the therapeutic preparations and methods available. For instance, in the monograph by Reifenstein on diseases of the parathyroid glands, in addition to an account of the action of parathyroid hormone secretions on calcium and phosphorous metabolism, the physiology and chemistry of bone, interrelationships between other hormones and minerals on bone, classification of all the metabolic bone diseases in adults and description of all the other disorders of parathyroid function are given.

The sections on the pituitary and thyroid by Williams, the adrenals and pancreas by Forsham and Thorn, the testes by Howard and Scott, the ovaries by George Smith, endocrine glands in relation to growth and development by Wilkins, neuroendocrinology by Friedgard, and obesity by Daughaday are equally extensive and informative. References are extensive and well arranged. The last two chapters, composed chiefly by Williams, delineate modern laboratory diagnostic and assay procedures and summarize treatment.

This book is no "primer" of endocrinology, no quick summary of current opinion for the rapid crammer. But for the reader who is seeking fundamental and authoritative guidance in this bewildering field it will be treasure worth the price of some midnight oil. Internists have come to expect outstanding performance from Robert Williams. He has not disappointed his fans in the second edition of his Textbook of Endocrinology.

PAUL S. RHOADS, M.D.

Cybernetics: Circular Causal and Feedback Mechanisms in Biological and Social Systems; Transactions of the Tenth Conference, April 22, 23, 24, 1953. Sponsored by Josiah Macy, Jr. Foundation. Edited by Heinz Von Foerster. Price, $2.75. Pp. 100, with 2 illustrations. Josiah Macy, Jr. Foundation Publications, 16 W. 46th St., New York 30, 1955.

With this volume, memorializing the tenth and final meeting of the Macy Foundation unit devoted to cybernetics, the present series of conferences underwritten by the Macy Foundation is at an end. This book is more valuable than some of the previous ones, which were only slightly edited stenotype reports of the actual give and take of the meetings. There is no question that such meetings are intensely stimulating to the participants. What is sometimes not so easily apparent, though it is perfectly obvious after a moment's thought, is that a play-by-play description of such conferences quickly reaches the point of diminishing returns for a reader. In this last volume, however, instead of a play-by-play account, there are individual essays with a very thoughtful foreward and appendix by Warren S. McCulloch.

At this turning point, it is well to back off a bit and think, not about this conference but about the degree to which any new generalization may be expected to develop and stimulate any field of our knowledge. To what extent may we expect to find actual illumination of the infinitely complicated and multifarious activities of the human central nervous system seen as the operation of electronic machines with controllable variables such as voltage, pressure, feed-

back, and such like. We hope that philosophers and thinkers will be sufficiently ahead of us to illuminate our thoughtful consideration and understanding of the world about us. But, with that hope, we must always keep in mind the danger of generalizations going far beyond actual data they are supposed to generalize and the tendency for any thinker who has approached the world with the insight of a new concept to try to fit more into his conceptual framework than it can possibly contain. We are all earnestly grateful for anything which throws an insight into the functioning of the central nervous system in man. Perhaps because of our traditional customs in using speech symbols, any new concept meets with a reaction which at times may be rather violent. This may help account for my belief that, in the present state of our comprehension of the functions of the central nervous systems, the conceptual approaches of model machines and cybernetics, while adding some insights, have left the problem largely unsolved. This criticism is tempered by the realization that in the simple but stark sense of the word solution is not to be expected. But we are grateful that such bold efforts go on.

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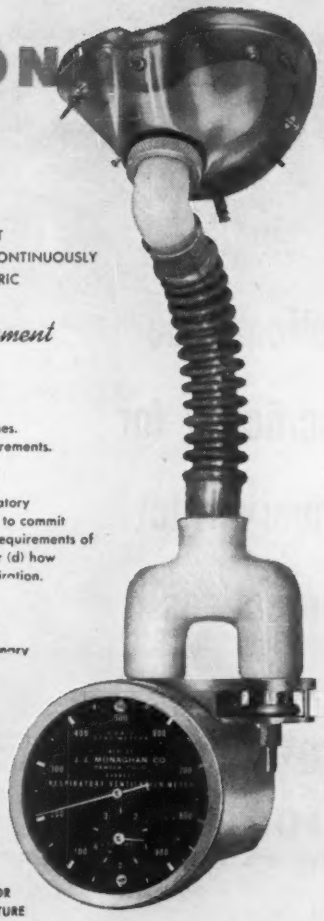

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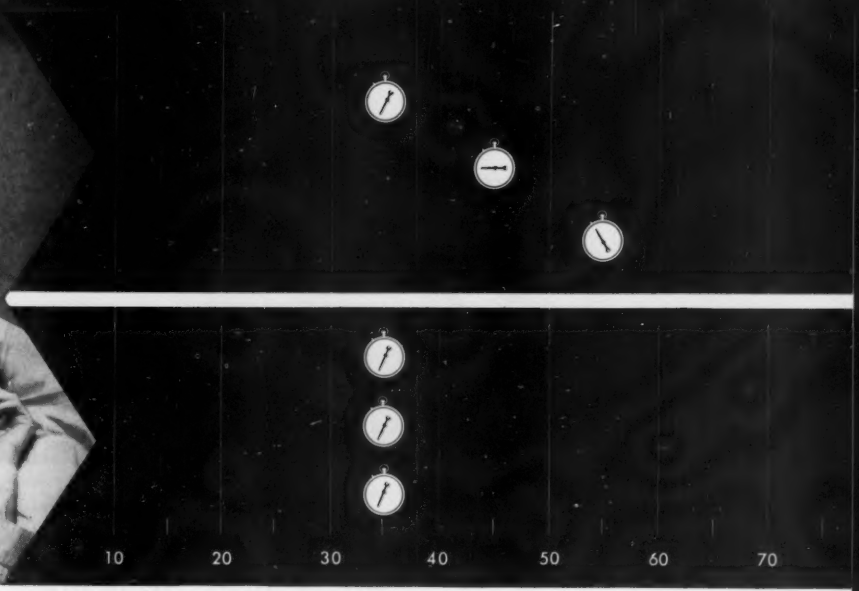

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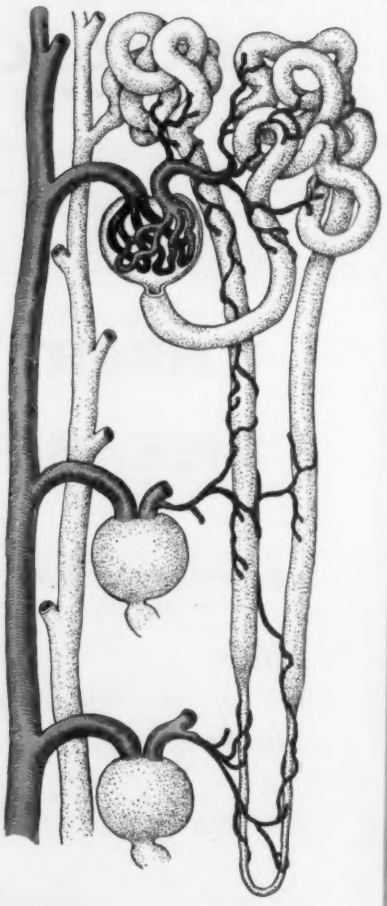

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Oral administration of Salyrgan-Theophylline tablets has become an established routine for interim diuresis — between parenteral administration — and for milder cases of edema and ascites. Patient response regulates the oral dosage.

SUPPLIED:

Ampuls of 1 cc. and 2 cc.—boxes of 10, 25 and 100.

Tablets —bottles of 100, 500 and 1000.

Another useful aid:

NEOCURTASAL®

Salt without Sodium

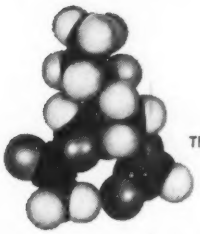
CONSTITUENTS: Potassium chloride, ammonium chloride, potassium formate, calcium formate, magnesium citrate, potassium iodide (0.01%) and starch.

2 oz. shakers • 8 oz. bottles

Winthrop LABORATORIES

NEW YORK 18, N.Y. • WINDSOR, ONT.

Salyrgan (brand of mersalyl) and Neocurtasal, trademarks reg. U. S. Pat. Off.



THE MILTOWN MOLECULE

A tranquilizer well suited for prolonged therapy

NO ORGANIC CONTRAINDICATIONS

reported to date

- well tolerated, non-addictive, essentially non-toxic
- no blood dyscrasias, liver toxicity, Parkinson-like syndrome or nasal stuffiness
- chemically unrelated to chlorpromazine or reserpine
- does not produce significant depression
- orally effective within 30 minutes for a period of 6 hours

Indications: anxiety and tension states, muscle spasm.

Miltown®

the original meprobamate—2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate—U.S. Patent 2,724,720

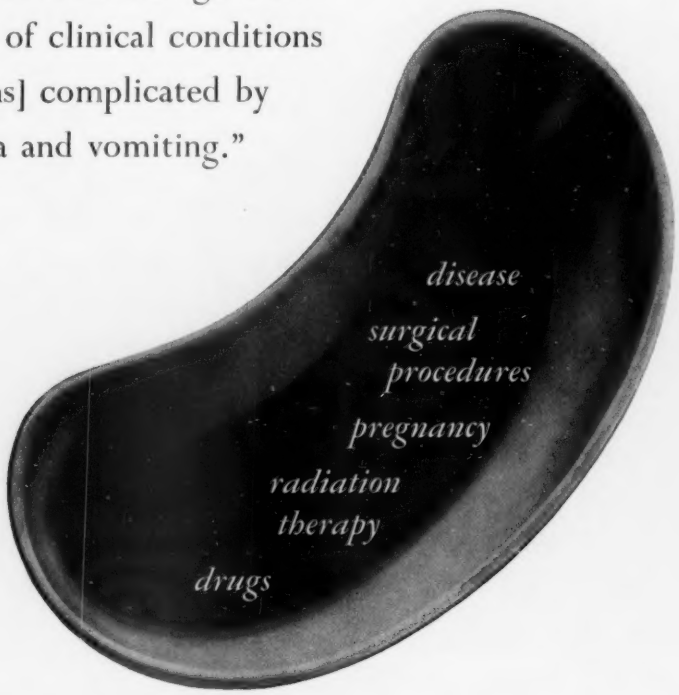
SUPPLIED: 400 mg. scored tablets. Usual dose: 1 or 2 tablets t.i.d.

DISCOVERED AND INTRODUCED by Wallace Laboratories, New Brunswick, N. J.

Literature and Samples Available on Request

THORAZINE*

"An effective antiemetic agent for a wide range of clinical conditions [and situations] complicated by nausea and vomiting."



1. Moyer, J.H., et al.: Arch. Int. Med. 95:202 (Feb.) 1955.

'Thorazine' is available in ampuls, tablets and syrup (as the hydrochloride), and in suppositories (as the base).

'Thorazine' should be administered discriminately and, before prescribing, the physician should be fully conversant with the available literature.

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.